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Global burden of acute lower respiratory infection (ALRI) associated with influenza virus, human metapneumovirus, and human parainfluenza virus among children under five years

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Declaration

I, Xin Wang, declare that the thesis has been composed by me and that the work has not be submitted for any other degree or professional qualification. I confirm that the work submitted is my own, except where explicitly stated otherwise and where work which has formed part of jointly-authored publications has been included. My contribution and those of the other authors to this work have been explicitly indicated below. I confirm that appropriate credit has been given within this thesis where reference has been made to the work of others.

The work presented in Chapter 4 has been accepted for publication as "Global burden of respiratory infections associated with seasonal influenza in children under 5 years in 2018: a systematic review and modelling study" in Lancet Global Health (in press), by Xin Wang (myself), You Li , Katherine L O'Brien, Shabir A Madhi, Marc-Alain Widdowson, Peter Byass, Saad B Omer, Qalab Abbas, Asad Ali, Alberta Amu, Eduardo Azziz-Baumgartner, Quique Bassat, W Abdullah Brooks, Sandra S Chaves, Alexandria Chung, Cheryl Cohen, Marcela Echavarria, Rodrigo A Fasce, Angela Gentile, Aubree Gordon, Michelle Groome, Terho Heikkinen, Siddhivinayak Hirve, Jorge H Jara, Mark A Katz, Najwa Khuri-Bulos, Anand Krishnan, Oscar de Leon, Marilla G Lucero, John P McCracken, Ainara Mira-Iglesias, Jennifer C Moïsi, Patrick K Munywoki, Millogo Ourohiré, Fernando P Polack, Manveer Rahi, Zeba A Rasmussen, Barbara A Rath, Samir K Saha, Eric AF Simões, Viviana Sotomayor, Somsak Thamthitiwat, Florette K Treurnicht, Marylene Wamukoya, Lay-Myint Yoshida, Heather J Zar, Harry Campbell (co-supervisor), and Harish Nair (supervisor). HN and HC conceptualised the study. I led the literature review with contributions from YL, AC, and MR. I led the data analysis with contributions from YL and M-AW. XW (myself), HN, HC, KLO'B, SAM, M-AW, PB, and SBO led the data interpretation. I wrote the first draft with input from HN, HC, KLO'B, SAM, M-AW, PB, and SBO. All other authors contributed to development of the analysis plan,

collection and analysis of primary data, data interpretation, and critically reviewed the revised initial manuscript. All authors read and approved the final draft.

The work presented in Chapter 5 and 6 was conceptualised by Harry Campbell (co-supervisor) and Harish Nair (supervisor). I led the literature review with contributions from Linda C Vaccari, You Li, and Kenneth McLean. I led the data analysis with contributions from You Li and Maria D Knoll. Xin Wang (myself), Harish Nair, Harry Campbell, Maria D Knoll, Shabir A Madhi, and Cheryl Cohen led the data interpretation. I wrote the draft with input from Harish Nair, Harry Campbell, Maria D Knoll, Shabir A Madhi, and Cheryl Cohen. All members of the Respiratory Virus Global Epidemiology Network contributed to development of the analysis plan, and collection and analysis of primary data.

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Lay summary of thesis

Influenza virus (IFV), human metapneumovirus (hMPV), and human parainfluenza virus (hPIV) are three important viruses causing acute lower respiratory infections (ALRI), including pneumonia and bronchiolitis. However, global burden estimates of hMPV-associated ALRI and hPIV-associated ALRI among young children are unavailable, and there are no licenced vaccines and approved antiviral treatment for the two viruses. Influenza virus has been the focus for many years. Some attempts have been made to estimate the global burden of influenza virus in children under five years using various types of data and different models over the past 10 years. The estimates for influenza virus vary across these studies, reflecting the methodological heterogeneity between studies. This thesis aims to estimate the global number of ALRI cases, hospitalisations, and deaths associated with the three viruses (IFV, hMPV, and hPIV) in children under five years.

This thesis uses data on virus–confirmed incidence rates, hospitalisation rates, and in–hospital case–fatality ratios (hCFRs) from systematic literature search and unpublished datasets shared by collaborators in the Respiratory Virus Global Epidemiology Network. This thesis also uses data on pneumonia deaths shared by the the Demographic Evaluation of Populations and their Health Network and the US Influenza–Associated Pediatric Mortality Surveillance System, and data on care–seeking among children with pneumonia as measured in Multiple Indicator Cluster Surveys and Demographic and Health Surveys.

This thesis estimates that globally, 9.1 million children under five years had IFV related ALRI infections in 2018, resulting in approximately 0.9 million hospitalisations and 27,400 deaths worldwide. Globally, 14.6 million children had hMPV related ALRI infections, resulting in 0.6 million hospitalisations and 16,100 deaths worldwide. Approximately 29.5 million children under five years had hPIV

related ALRI infections, resulting in 1.0 million hospitalisations and 53,000 deaths worldwide. Age–stratified estimates show that infants had higher hospitalisation rates than older children, and 45–61% of the hospitalisations (varying by viruses) occurred among infants under one year old. Children in low– and lower middle–income countries had higher hCFRs than other countries.

These estimates demonstrate that globally, IFV, hMPV, and hPIV contribute to 7%, 11%, and 21% of ALRI cases and contribute to 3%, 2%, and 7% deaths due to ALRI in children under five years. This thesis uses data on cause of child ALRI death from Child Health and Mortality Prevention Surveillance Network in sensitivity analysis for mortality estimation. Additional data on incidence rates, hospitalisation rates, and hCFRs of virus–confirmed ALRI by narrow age groups would refine the estimates. Using existing influenza surveillance systems and new surveillance systems may help improve the availability of data on hMPV and hPIV disease burden (especially hospitalisations) and the activity of the two viruses. Virus–ALRI mortality estimates would be refined by improving the viral etiologic diagnosis in children who die from ALRI outside hospital inpatient services. Ongoing and new post–mortem surveillances would help refine the mortality estimates in the future.

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Abstract

Introduction

Acute lower respiratory infection (ALRI) is one of the leading causes of mortality in children under five years. Although childhood ALRI mortality has substantially reduced over the past 15 years, continued progress will in part depend on targeted prevention and treatment against important pathogens in future. Influenza virus (IFV), human metapneumovirus (hMPV), and human parainfluenza virus (hPIV) are three important viruses causing childhood ALRI. However, global burden estimates of hMPV-associated ALRI and hPIV-associated ALRI among young children are unavailable, and there are no licenced vaccines and approved antiviral treatment for the two viruses. Over the past 10 years, several studies have estimated the global burden of influenza virus in young children using different types of data and different models. The estimates varied between these studies, partly reflecting the differences in analytical models between studies. This thesis aimed to estimate the global and regional ALRI morbidity and mortality associated with the hMPV and hPIV, and to update the estimates for global and regional ALRI burden associated with IFV.

Methods

Systematic reviews were conducted to identify published data on IFV-associated, hMPV-associated, hPIV-associated ALRI burden among children under five years. Relevant data included laboratory-confirmed incidence rates, hospitalisation rates, proportion positives, and in-hospital case-fatality ratios (hCFRs). Additionally, Respiratory Virus Global Epidemiology Network contributed unpublished data by finer age groups from different geographic locations, especially from low- and lower middle-income countries experiencing high childhood ALRI burden. A modified Newcastle-Ottawa Scale was used to assess the risk of bias in included studies. Incidence rates, hospitalisation rates,

proportion positives, and hCFRs of virus-associated ALRI were analysed using a generalized linear mixed model. The meta-estimates of incidence rates and hospitalisation rates were applied to United Nation 2018 population estimates to yield the number of cases and hospitalisations of virus-associated ALRI. The point estimates and uncertainty ranges were estimated using Monte Carlo simulation. The hospitalisations and hCFRs for virus-ALRI were combined to yield the estimates for in-hospital mortality. Analyses were stratified by three age groups (0-5 months, 6-11 months, and 12-59 months) and child mortality settings (low and high) where available. Data were also stratified by World Bank income regions and country development status. The overall virus-associated ALRI deaths (including both in-hospital and out-hospital deaths) were estimated using in-hospital mortality estimates and multiple types of data due to the differences in data availability for the three viruses. These data mainly included population-based childhood pneumonia deaths in defined catchment areas, care-seeking for child pneumonia, and the US influenza-associated paediatric in-hospital deaths and out-hospital deaths.

Results

Globally among children under five years, IFV was associated with 9.1 million (UR 6.4–13.2) ALRI cases, 854,000 (UR 514,000–1,450,000) hospitalisations, 27,400 (UR 10,600–100,000) ALRI deaths, accounting for 7% of ALRI cases, 5–17% of ALRI hospitalisations, and 3% of ALRI deaths. hMPV was associated with 14.6 million (UR 10.5-21.0) ALRI cases, 643,000 (UR 425,000–977,000) ALRI hospitalisations, 16,100 (UR 5,700–88,000) ALRI deaths, accounting for 11% of ALRI cases, 4–13% of ALRI hospitalisations, 2% of ALRI deaths. hPIV was associated with 29.5 million (UR 19.2–46.7) hPIV–ALRI cases, 1.0 million (UR 0.6–1.8) ALRI hospitalisations, and 53,000 (UR 25,300–113,500) ALRI deaths, accounting for 21% of ALRI cases, 6–20% of ALRI hospitalisations, 7% of ALRI deaths. The three viruses shared several similarities in the burden distribution. For the three viruses, infants had higher hospitalisation rates than

older children. About 45–61% of the virus–ALRI hospitalisations occurred among infants under one year old (varying by viruses). hCFRs varied by income regions, and children in low– and lower middle–income countries generally had the highest hCFRs. The differences in hCFR meta–estimates of IFV–ALRI and hPIV–ALRI between age groups was less obvious than hMPV–ALRI. For hMPV–ALRI, the hCFRs were much higher in young infants aged 0–5 months than older children.

Conclusion

These estimates show that the three viruses are associated with substantial burden in children under five years. Infants under one year old and children in low– and lower–middle income countries were disproportionately affected by severe infections associated with the three viruses. This thesis presented the new IFV–associated ALRI morbidity and mortality estimates in the era with the circulation of influenza A/H1N1pdm09, and the first global burden estimates of hMPV–ALRI and hPIV–ALRI in children under five years, by narrow age groups. These global and regional burden estimates should inform the development of targeted prevention and treatment and guide further health investment priorities and resource allocation. The IFV–associated burden estimates should provide new evidence for maternal and paediatric influenza immunisation and should inform future immunisation policy particularly in low– and middle–income countries as a national influenza immunisation programme has not been adopted in most low– and lower middle–income countries. Large data gaps exist, especially in the mortality of virus–ALRI. Continued efforts are needed to fill and address the data gaps to improve global burden estimates providing evidence for developing future prevention and treatment strategies against childhood ALRI.

Chapter 1 Background

1.1. Acute lower respiratory infection

Acute lower respiratory infections (ALRI), including bronchiolitis and pneumonia, are one of the leading causes of morbidity and mortality in children worldwide, accounting for 10% of mortality in children under five years in 2017 (WHO 2018). Globally, there were 68–138 million ALRI cases and 5–16 million ALRI hospitalisations in children under five years during 2015–2016 according to studies (McAllister et al. 2019, Troeger et al. 2018). Infants, especially neonates, are at greater risk of ALRI hospitalisation and mortality compared with older children (Nair et al. 2013, Li Liu et al. 2016). Hypoxaemia (oxygen saturation below 90%) and general danger signs (i.e., difficulty in breastfeeding or drinking, vomiting everything, convulsions, lethargy, or unconsciousness, cyanosis, head nodding) are indicators of increased severity and mortality (WHO 2005a, Lazzerini et al. 2015). Findings from a systematic review suggest that children with oxygen saturation below 90% have a 5.4 fold increase in the risk of death from ALRI (Lazzerini et al. 2015). Among children under five years, about 11–15% of hospitalised ALRI presented hypoxaemia (varying by age), and 25% of hospitalised ALRI presented with either danger signs or hypoxaemia (Nair et al. 2013). As recommended by World Health Organization (WHO) Integrated Management of Childhood Illness (IMCI), the presence of a general danger sign indicates the need for urgent referral (WHO 2005a). Although screening and management of hypoxaemia was not emphasized in the guidelines, evidence shows that oxygen therapy and systematic screening for hypoxaemia using pulse oximetry can substantially reduce the risk of mortality (Floyd et al. 2015, Subhi et al. 2009).

Viruses are important causes of childhood ALRI, accounting for 61% of hospitalised ALRI in children under five years according to one recent prospective, multi–country pneumonia case–control study (Pneumonia Etiology

Research for Child Health Study Group (PERCH) 2019). Respiratory syncytial virus (RSV), influenza virus (IFV), human metapneumovirus (hMPV) and human parainfluenza virus (hPIV) are the leading causative viruses of childhood ALRI (Shi et al. 2015, Benet et al. 2017, Zar et al. 2016, Pneumonia Etiology Research for Child Health Study Group (PERCH) 2019). ALRI caused by different viruses have similar symptoms, so are not distinguishable by clinical presentation (Ma et al. 2018). The diagnosis of a virus depends on the identification of the virus using laboratory tests. The advent of molecular tests allows us to identify traditional and emerging viruses, and improves our understanding of these viruses (Mahony 2008). Next sections summarise the key characteristics of the structure of three viruses – IFV, hMPV, and hPIV, and the epidemiology, prevention, and treatment of the infections associated with the three viruses.

1.2. Influenza virus (IFV)

1.2.1. Basic description of influenza virus

Influenza viruses (IFV), belonging to Orthomyxoviridae family, are negative–sense, single–stranded and segmented RNA viruses. There are four types: influenza A, B, C, and D. Influenza A and B cause clinically important disease in human populations (Ghebrehewet et al. 2016). IFVA are further divided into subtypes based on the antigenic differences of the two most important surface proteins: hemagglutinin (HA) and neuraminidase (NA). There have been 18 hemagglutinin subtypes and 11 different neuraminidase subtypes described so far (Webster et al. 1992, Bouvier and Palese 2008, US Centers for Disease Control and Prevention 2017). Influenza B viruses are divided into two lineages: B/Yamagata and B/Victoria (Hay et al. 2001).

IFV is constantly changing through two mechanisms – antigenic drift and antigenic shift (Fukuyama and Kawaoka 2011). The accumulation of mutations during genomic replication contributes to the minor and gradual changes in virus

proteins (“antigenic drift”). These changes allow the virus to evade pre–existing immunity and to cause reinfections and annual epidemics (Bouvier and Palese 2008, Ghebrehewet et al. 2016). In contrast, the emergence of a new influenza A subtype due to a major shift in the surface proteins (“antigenic shift”) causes pandemics as most people have no immunity against the new subtype. The most recent influenza pandemic in 2009 was caused by a new influenza A subtype – A/H1N1pdm09, which is different from the pre–existing seasonal A(H1N1) virus. The new subtype has replaced the old subtype and has been circulating annually since the 2009 influenza pandemic (WHO 2019).

IFV mainly spreads by infectious droplets and aerosols and replicates in endothelial cells in the respiratory tract (Wagner et al. 2002, US Centers for Disease Control and Prevention , WHO , Killingley and Nguyen-Van-Tam 2013). A systematic review (Lessler et al. 2009) estimated that the incubation period (the time between infection and symptom onset) for IFV ranged from 1 to 4 days, with the median incubation period of 1.4 days for type A, and 0.6 days for type B. Virus shedding generally peaks within the first three days after illness onset (Lau et al. 2010). Healthy children can shed virus for up to two weeks after illness onset, with viral load decreasing with time. Children with weakened immune systems may have a longer shedding time (Carrat et al. 2008, Lau et al. 2010).

1.2.2. Epidemiology, prevention, and treatment

Seasonal influenza epidemics often occur in winter and spring in temperate climate regions, while the seasons are less defined in subtropical or tropical climate regions. For temperate climate regions, seasonal influenza epidemics occur during October–June, with peaks around January and February in northern hemisphere; in southern hemisphere, seasonal influenza epidemics occur during May–October, with peaks around August (WHO). The circulation of influenza is generally low outside seasons in temperate climate regions. In

tropical climate regions, influenza may occur throughout a year, with one or multiple peaks; the timing of influenza epidemics varies across years and regions. The seasonality of influenza is found to be shaped by temperature and humidity, though the mechanism remains unclear (Lowen and Steel 2014, Jaakkola et al. 2014, Cherry et al. 2009, Li et al. 2019, Broor et al. 2012). The activity of influenza virus, especially A(H3N2), is positively associated with low temperature and high relative humidity according to one systematic analysis on the global pattern of influenza virus (Li et al. 2019). Consistent with this, another systematic analysis shows that seasonal influenza epidemics are associated with two types of environmental conditions – “cold–dry” and “humid–rainy”. In details, influenza activity peaks during the cold-dry season for locations with low level average humidity or temperature, while for locations with high level average humidity and temperature, the activity peaks during rainy season (Tamerius et al. 2013).

Influenza A has been documented to cause several pandemics (2010, Kilbourne 2006), and the most recent pandemic was caused by A/H1N1pdm09 during 2009–2010. It was estimated that the 2009 global pandemic respiratory mortality burden in all ages was similar to seasonal influenza (Dawood et al. 2012, Simonsen et al. 2013). However, several studies suggest the age distribution of A/H1N1pdm09–associated burden differs from that of seasonal influenza. Several US studies found that the median age of children who died from A/H1N1pdm09 was higher compared with the children who died from seasonal influenza (Ruf and Knuf 2014). Similarly, a pooled analysis of data from 19 countries or regions suggested the risk of hospitalisations due to A/H1N1pdm09 was the same for 0–4 years and 5–14 years (Van Kerkhove et al. 2011). Influenza B viruses are less common in most seasons than influenza A viruses, and do not cause pandemics. The virology data from 31 countries showed that IFVB accounted for 23% of all influenza infections during 2000–2018, and was the dominant virus type in one every seven seasons (Caini et al. 2019).

In addition to respiratory illnesses, influenza can also cause many extra–pulmonary complications, such as myocarditis and encephalitis (Ghebrehewet et al. 2016). Recently, emerging evidence shows that influenza infections are associated with the occurrence of acute myocardial infarction in older people (Steinberg et al. 2012, Barnes et al. 2015, Surtees and DeSousa 2006).

Influenza vaccination protects people from influenza infections. The protective effect of influenza vaccines varies, and depends on the degree of match between the vaccine and circulating influenza strains, and individuals' susceptibility to infection and their responses to vaccination (US Centers for Disease Control and Prevention). Children aged 6 months–59 months are recommended as one of the priority groups for seasonal influenza vaccination. According to systematic reviews, the efficacy of trivalent inactive influenza vaccine (TIV) can be 58% against laboratory–confirmed influenza infections in children aged 6 months to 7 years, and the efficacy can be 83% for the live attenuated influenza vaccine (LAIV); the included data were mostly from seasons with a good match between the epidemic and the vaccine strain (Jefferson et al. 2005, Osterholm et al. 2012, Manzoli et al. 2012). Inactive influenza vaccine is recommended for children aged 6 months to 2 years. However, the efficacy of TIV is generally low for this age group (Rolfes et al. 2017, Jefferson et al. 2005). In a randomized trial among children of Germany and Finland, the MF59–adjuvant trivalent influenza vaccine (MF59 is an oil-in-water emulsion adjuvant that arguments the immune responses) showed greater efficacy against laboratory–confirmed influenza infections compared with TIV [77% (95%CI 37 to 92) versus 11% (95%CI 58 to 89)] in young children aged 6 months to 2 years during two seasons with a good matching (at least 85% of cases were caused by the vaccine-matched strains) (Vesikari et al. 2011). Maternal vaccination increases the level of maternal antibodies transferred to newborns, thus, protecting infants younger than 6 months from influenza infections (Marta C. Nunes and Shabir A. Madhi 2018). Maternal influenza

vaccination could prevent 48% of laboratory–confirmed influenza infections and 72% of laboratory–confirmed hospitalisations in the first 6 months of life according to results from four trials (M. C. Nunes and S. A. Madhi 2018). Studies in high–income countries have shown similar effects of maternal influenza immunisation. Pooled analyses of data from several observational studies from US and UK suggested that maternal vaccine could reduce 58% of laboratory–confirmed influenza infections and 82% of laboratory–confirmed hospitalisations in the first six months of life (M. C. Nunes and S. A. Madhi 2018). The degree of match between the vaccine and the circulating influenza strains was usually not reported in the included studies.

Neuraminidase inhibitors, including inhaled zanamivir and oral oseltamivir, were recommended to treat children with severe infections during the 2009–2010 influenza pandemic (WHO 2010). However, the policies on the use of neuraminidase inhibitors varied across countries (Muthuri et al. 2014). Zanamivir is indicated for people aged above five years (WHO 2010). Oseltamivir is licensed to treat influenza infections in young children. It is recommended that young children, especially those under two years, and those who are at greater risk of developing severe complications from pandemic influenza, should be treated with oseltamivir as soon as possible in the infection. Oseltamivir can reduce the duration of illness and lower the risk of developing otitis media (Malosh et al. 2017). Prompt treatment within the first 48 hours of symptom onset can reduce over 50% of mortality risk in children who are critically ill with influenza (Louie et al. 2013). For young children, vomiting is the only adverse effect potentially associated with the use of oseltamivir (Malosh et al. 2017).

1.3. Human metapneumovirus (hMPV)

1.3.1. Basic description of hMPV

Human metapneumovirus (hMPV) was first identified in 2001 in Netherlands (Van den Hoogen et al. 2001). Belonging to the Paramyxoviridae family along

with RSV, it is an enveloped, single–stranded, negative–sense RNA virus (Kahn 2006, Schuster and Williams 2013). There are two major genetic subgroups, A and B, each with two minor subgroups (A1, A2, B1, and B2) (Van den Hoogen et al. 2004, Yang et al. 2009). Cross–protection against different strains may exist, but the immunity wanes over time (Principi et al. 2006, Schuster and Williams 2013). Studies have reported hMPV reinfections in young children, usually with a different subgroup; reinfection is usually milder (Williams et al. 2004, Ebihara et al. 2004).

Like other respiratory viruses, hMPV spreads mainly by respiratory droplets and secretions. The incubation period ranges from 4 to 6 days for hMPV (Lessler et al. 2009). Viral shedding can last one to two weeks after acute illness onset (Panda et al. 2014, Sarasini et al. 2006, Nina Moe et al. 2017).

1.3.2. Epidemiology, prevention, and treatment

In most temperate climate regions, hMPV epidemics occur in late winter and spring, while the timing of epidemics is more diverse in the tropics (Kahn 2006, US Centers for Disease Control and Prevention , Li et al. 2019, Owor et al. 2016, Gardinassi et al. 2012, Do et al. 2011). The activity of hMPV was found to be significantly associated with the RSV activity in most temperate climate regions, with the epidemics occurring 1–2 months later than RSV (Li et al. 2019). The association between hMPV and RSV epidemics have been studied in a temporal analysis in UK (Nickbakhsh et al. 2019). This study found a positive interaction among hMPV and RSV activity at population level, while was unable to assess this interaction at host level due to the small number of hMPV cases. Future studies are warranted to improve the understanding of such interaction, for example, whether this interaction is the result of viruses' different responses to certain environment conditions, including temperate and humidity, or their responses to population immunity dynamics, or both (Nickbakhsh et al. 2019). The timing of hMPV epidemics can vary by years. One study in the US

observed that hMPV epidemics demonstrated a unique biennial pattern of early and late seasonal onsets, following RSV seasons (Haynes et al. 2016). Different subgroups of hMPV usually co–circulate, with the subgroup A2 and B2 more frequently detected (Aberle et al. 2010, Loo et al. 2007). One study among Austrian infants hospitalized with acute respiratory infections (ARI) observed a periodic change in the predominate subgroup – one dominating hMPV subgroup was displaced by another subgroup every 1 to 3 years during 1987–2008. This displacement might reflect the dynamics of population immunity against heterologous and homologous subgroups (Aberle et al. 2010). A similar finding was reported in one study among US children under five years with upper respiratory infections (URI) during 1982–2001 (Williams et al. 2006). In contrast, one study in Kilifi, Kenya observed that the subgroup A2 dominated solely through four years during 2007–2011, with the other subgroups (B2) co–circulating in lower numbers (Owor et al. 2016). There is no consistent evidence about the relationship between hMPV subgroups and disease severity (Wei et al. 2013, Panda et al. 2014, Schuster et al. 2015, N. Moe et al. 2017).

Being closely related to RSV, hMPV shares some similarities in clinical symptoms with RSV (Garcia-Garcia et al. 2017, N. Moe et al. 2017, Edwards et al. 2013). For example, bronchiolitis and wheezing are more commonly associated with hMPV compared to other viruses (Williams et al. 2004, Panda et al. 2014, Bosis et al. 2005). However, the age distribution of hMPV infections is different from RSV infections. In the community setting, the rate of hMPV infections is greater in children aged 6–11 months (Homaira et al. 2012, Edwards et al. 2013). In contrast, the age distribution of hMPV infections is more variable in hospital settings. The highest hospitalisation rate of hMPV respiratory infections was observed among 0–5 months in some studies (Edwards et al. 2013, Homaira et al. 2016), while among 6–11 months in others (Owor et al. 2016).

Currently there are no approved antiviral treatments or licenced vaccines for hMPV infections (Luoto et al. 2016, Panda et al. 2014). Supportive care is provided to relieve the symptoms caused by severe infections. Some strategies have been tested in vitro and in animal models for the treatment and control of hMPV infections, such as antiviral (ribavirin), polyclonal antibody, monoclonal antibody, and fusion inhibitors (Panda et al. 2014, Wen and Williams 2015). Ribavirin and intravenous immunoglobulin have been administered to patients with severe hMPV infections (Wen and Williams 2015). Several types of hMPV vaccine candidates have been developed and tested in animal models, such as inactivated vaccines, subunit vaccines, and live–attenuated vaccines. Inactivated vaccines have been reported to cause enhanced disease after hMPV infections. Subunit vaccines can induce immune responses, but the responses wane quickly over time (Shafagati and Williams 2018). Live–attenuated vaccines have showed promise in animal models by inducing high titres of neutralizing antibodies that protected against hMPV challenge (Wen and Williams 2015). A live–attenuated recombinant hMPV vaccine has been assessed in a recent phase I clinical trial, though the results showed that the vaccine was over–attenuated for children aged 6–59 months (San Mateo et al. 2017).

1.4. Human parainfluenza virus (hPIV)

1.4.1. Basic description of hPIV

Human parainfluenza virus (hPIV) was first identified in children in the 1950s (Chanock and Parrott 1965). hPIV belongs to the Paramyxoviridae family, together with RSV and hMPV (Bennett et al. 2014). There are four predominant serotypes (hPIV–1 to hPIV–4) causing disease in human population, divided into Respirovirus (hPIV–1 and hPIV–3) and Rubulavirus (hPIV–2 and hPIV–4) genera. There are two major subtypes of hPIV–4 (hPIV–4A and hPIV–4B) (Henrickson 2003). Parainfluenza virus 5 cause diseases in cattle, but not in the

human population (Y. Liu et al. 2015). Like other respiratory viruses, hPIV spreads by respiratory droplets. According to a systematic review, the incubation period for hPIV ranges from 2 to 6 days, with a median period of 2.6 days (Lessler et al. 2009). Infected children can shed virus from 3–4 days before the onset of symptoms to 10 days past; the period can be longer for hPIV–3 (Henrickson 2003). Reinfections have been described in children, reflecting waning immunity (Glezen et al. 1984, Henrickson 2003).

1.4.2. Epidemiology, prevention, and treatment

HPIV epidemics are mostly in spring and early summer in northern and southern hemispheres, with a longer duration (6–7 months) of epidemics than IFV and hMPV (Li et al. 2019). The seasonal patterns of hPIV vary by serotypes. HPIV–3 is the most frequent serotype; increased activity has been seen in spring, summer, and autumn. HPIV–1, hPIV–2, and hPIV–4 are less frequent, and their seasonality is less defined (Henrickson 2003, US Centers for Disease Control and Prevention 2015, Abedi et al. 2016, Liu et al. 2013, Mizuta et al. 2013). In tropics, hPIVs can circulate throughout the year (Morgan et al. 2013, Fé et al. 2008, Khor et al. 2012).

The age distribution and clinical manifestations vary by hPIV serotypes. HPIV–3 tends to infect young infants (i.e., under 6 months) while hPIV–1 and hPIV–2 tend to infect older children (1–3 years). ALRI can be caused by all serotypes, but more frequently caused by hPIV–3. HPIV–1 and HPIV–2 are common causes of croup (Henrickson 2003, Liu et al. 2013, Weinberg et al. 2009, Abedi et al. 2014). It is believed that hPIV–4 usually causes mild illness in children, and partly because of this perception, hPIV–4 is rarely included in the routine respiratory virus detection (Aguilar et al. 2000, Lau et al. 2005). However, several studies from different populations have showed hPIV–4 is more frequent than hPIV–2 among children hospitalised with respiratory infections (Maykowski et al. 2018, Frost et al. 2014, Xiao et al. 2016, Linster et al. 2018). Inconsistent

findings were reported on the association between severity and different hPIV serotypes (Maykowski et al. 2018, Frost et al. 2014, Xiao et al. 2016, Linster et al. 2018).

Like hMPV, there are no specific antiviral treatments or licenced vaccines for hPIV infections currently. The development of hPIV vaccines has started since 1960s. Cross protection between different serotypes is minimal and short–lived (Branche and Falsey 2016). Currently, most research has been focused on hPIV–3 vaccines, which is the predominant serotype and the serotype most commonly detected in children with pneumonia. Three hPIV–3 candidate vaccines have been assessed or are currently under assessment in phase I and phase II clinical trials among children (rHPIV3rcp45, rB/HPIV3, and MEDI–534), and two have demonstrated safety and immunogenicity in seronegative children older than 6 months (Karron et al. 2011, Bernstein et al. 2011, Bernstein et al. 2012). Moreover, studies show that a 3 dose–schedule (2 doses administrated 2 months apart) can increase the antibody levels of recipients following each dose (Bernstein et al. 2011, Bernstein et al. 2012). A longer interval between doses (2 doses administrated 6 months apart) can boost the antibody titres in the recipients with a suboptimal response after the prior dose (Englund et al. 2013). A few vaccines against hPIV–1 and hPIV–2 infections are now in phase I clinical trials in children (Karron et al. 2014, Adderson et al. 2015, Schmidt et al. 2011).

1.5. Risk factors

There are a wide range of risk factors associated with greater rates of ALRI, increased disease severity, and an increased risk of death from ALRI. Child related factors include younger age (under 6 months), prematurity, malnutrition, low birthweight, lack of exclusive breastfeeding, and immunodeficiency (Sonego et al. 2015, Jackson et al. 2013, Rudan et al. 2008, Rudan et al. 2013). In addition, there are socioeconomic, environmental and healthcare–related factors, such as low maternal education and low socioeconomic status,

crowding, passive smoking, indoor air pollution, incomplete immunization, access to care, and quality of care (Sonego et al. 2015, Rudan et al. 2008, Jackson et al. 2013). The presence of chronic underlying diseases has also been reported to increase the risk of death from ALRI in children (Sonego et al. 2015).

For specific pathogens, studies have been focused on the risk factors of RSV– and IFV–associated ALRI (T. Shi et al. 2015). Younger age (under 2 years), a history of prematurity, immunodeficiency, the presence of specific comorbidities (e.g., chronic respiratory disease, chronic cardiac disease, and compromised immune status) are important risk factors related to severe influenza infections in children (WHO Strategic Advisory Group of Experts on Immunization 2012, Gill et al. 2015).

Few studies have assessed the risk factors for hMPV– or hPIV–specific infections in children. Similar to all–cause ALRI, the presence of underlying chronic diseases (e.g., chronic respiratory and cardiac disease) are related to greater rates of hMPV– and hPIV–respiratory infections, and increased severity among infected children (Hahn et al. 2013, Cohen et al. 2015, Papenburg et al. 2012, Principi and Esposito 2014, Henrickson 2003, Schuster and Williams 2013, Madhi et al. 2007, Maykowski et al. 2018, Mullins et al. 2004). Several studies show that prematurity is an important risk factor for hMPV infections in children. Prematurity is associated with greater hMPV respiratory hospitalisations. In a 7–year prospective study of Spanish children hospitalised with ALRI, hMPV was more frequently detected in preterm children than in term children (P–value <0.05), while the difference was not significant for IFV or RSV (Garcia-Garcia et al. 2015). Similar findings were also reported in other prospective studies (Edwards et al. 2013, Papenburg et al. 2012). Moreover, hMPV–infected children with a history of prematurity are more likely to need

supplemental O2, to have subcostal retractions, and to stay longer in hospitals compared with those without (Pancham et al. 2016).

The association of human immunodeficiency virus (HIV) infections and hMPV and hPIV infections has been studied in African population. In a prospective severe acute respiratory infection (SARI) surveillance in South Africa, the hospitalisation rate of hPIV–SARI was 1.5–3.7 times greater in children with HIV infections compared with children without (Cohen et al. 2015). Of note, the greater rate of hospitalisations for viral infections does not suggest a greater contribution of viruses among HIV–infected children. A systematic review among African population did not find significant difference in the percent positivity of hPIV in ALRI between HIV positive and HIV negative children aged 0–5 years [Odds ratio (OR), 1.38 (95%CI 0.73–1.26)] (Kenmoe et al. 2019). In the same study, however, hMPV was detected less frequently among HIV positive children than HIV negative children [OR, 0.50 (95%CI 0.40–0.60)]. The lower aetiology of hMPV in HIV–infected children is consistent with hospitalisation data. Although HIV is known to be associated with greater hospitalisation rates of all–cause SARI, one study estimated similar hospitalisation rates of hMPV–associated SARI in HIV–infected and HIV–uninfected children under five years. The association of HIV infections and the severity of hMPV and hPIV infections is controversial. According to two studies, HIV–infected children had prolonged hospitalisations and an increased risk of death (Madhi et al. 2002, Madhi et al. 2007). However, this association might be confounded by the greater prevalence of bacterial coinfections and underlying diseases in HIV–infected children. Another study adjusted for the presence of pneumococcal coinfection and other factors (age and hospital site) and did not find the association between HIV infections and longer hospital stays or increased risk of deaths from hPIV–SARI among children under five years (Cohen et al. 2015). However, the small number of outcomes (e.g., deaths) in this study might have limited its ability to detect an association.

Infants, especially those under six months, are more susceptible to severe respiratory infections and deaths from respiratory infections than older children (Nair et al. 2013, Zhou et al. 2012, Sachedina and Donaldson 2010, Abedi et al. 2014, Weinberg et al. 2009, Edwards et al. 2013). The increased susceptibility is related to the immaturity of their immune system (Simon et al. 2015). Figure 1–1 shows the immune response to influenza infections over the lifetime of an individual (Simon et al. 2015). As shown in Figure 1–1, new-borns have a relatively high level of immune response to influenza at birth because maternal antibodies are transferred to the baby across the placenta and through breastfeeding, providing protection in early life. However, maternal antibodies decay over time in infants and infants are increasingly exposed to infectious agents through contact . Human immune system develops gradually and reaches adult levels at around the 20th year.

The duration of protection that maternally acquired antibodies may provide may vary depending on viruses. Natural maternal antibodies may only protect against influenza infections for less than one week without maternal immunisation (M. D. Tapia et al. 2016, Nunes et al. 2016). Similarly, maternal antibodies against hMPV and hPIV infections decay in the first several months of life, as shown in prospective studies (Fadeela et al. 2003, Sangli et al. 2001).

Maternal antibody and the immature immune system impede active immunization in early life. In the presence of maternal antibodies, the protective immune response of young infants (e.g., the antibody response) is inhibited after active vaccination; in theory vaccinating infants would only be successful after the maternal antibody levels decline below a certain threshold (Niewiesk 2014). This gives rise to an important vaccination strategy – maternal immunisation, protecting from respiratory infections in early life. Vaccinating pregnant women increases the amount of antibodies in both pregnant women and newborns, and higher titres of maternal antibodies can protect infants for a longer duration.

Maternal influenza immunisation can prevent around 48% of mild influenza infections and 20% of all–cause ALRI hospitalisations in the first 6 months of life (Omer et al. 2018, M. C. Nunes and S. A. Madhi 2018). The duration of protection conferred by maternal influenza vaccination varies between trials. Trivalent inactive influenza vaccine (TIV) reduced the risk of influenza infections throughout the first four months of life among Mali infants, while the protection only lasted for the first eight weeks of life in South African infants. Factors affecting the protection duration need to be explored.

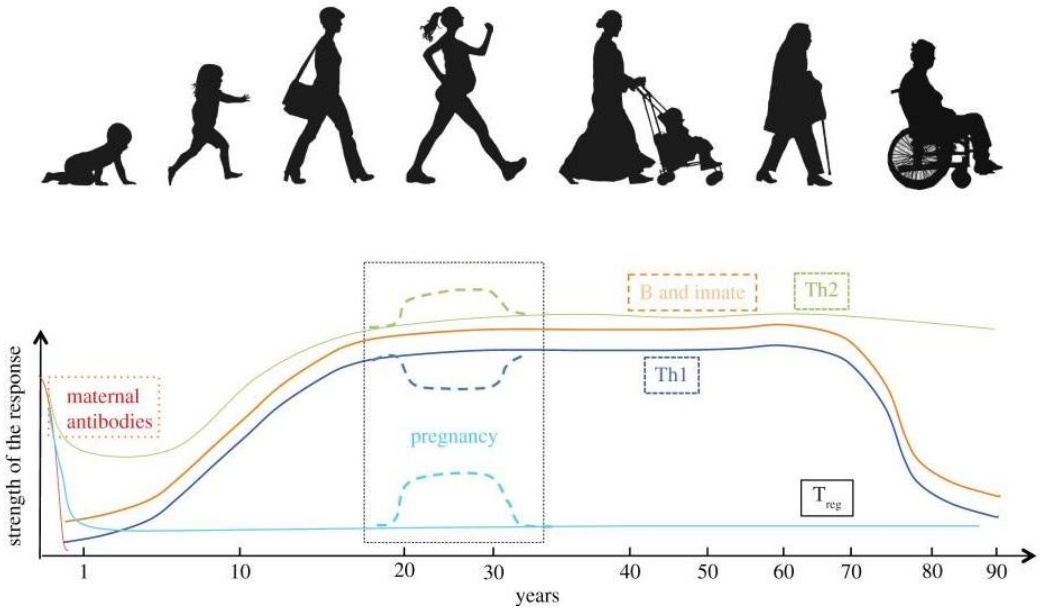

Figure 1–1. The seven ages of woman and a schematic graph of the different arms of the immune response to influenza over the lifetime of an individual

Upper: seven ages of women; below: different arms of the immune response. Figure from (Simon et al. 2015) *.

1.6. Specimens and diagnostic tests

Since clinical manifestations of ALRI are nonspecific, it is often difficult to differentiate between viral and bacterial ALRI, or to distinguish ALRI caused by one virus from other viruses. Thus, an accurate and quick diagnosis depends on the identification of a particular virus, and can inform case management in clinical settings. Collection of specimens in the early course of illness, collection of nasopharyngeal specimens, storage at an appropriate temperature, immediate transport to the laboratory, and detecting with a high-accuracy test method are critical for producing reliable test results (Ginocchio and McAdam 2011).

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There are many tests available for detecting IFV, hMPV, and hPIV, including virus culture, immunofluorescence assays, including direct fluorescent antibody assay (DFA) and indirect fluorescent antibody assay (IFA), molecular assays such as reverse transcription–polymerase chain reaction (RT–PCR), and influenza rapid tests. Molecular assays have been considered the best method because of their accuracy and rapidity in detecting viruses, and the ability to identify subtypes (Templeton et al. 2005, Landry 2011). Compared with molecular assays, other tests are less sensitive in detecting viruses, and are usually more affected by the specimen quality. Moreover, some tests rely on substantial expertise, thus the sensitivities and specificities are variable between laboratories (Landry 2011). The sensitivity of a test compared with molecular assays can vary by viruses (Mahony 2008, Ginocchio and McAdam 2011). For example, DFA is approximately 70–98% sensitive in detecting seasonal IFV, 47–93% for A/H1N1pdm09, and 38–80% for hMPV compared with molecular assays (Jokela et al. 2010, Wolf et al. 2015, Jun et al. 2008, Aslanzadeh et al. 2008, Landry 2011, Mahony 2008). Similarly, molecular assays are much more sensitive in detecting hPIV, especially hPIV–4, than cell culture and IFA (Lau et al. 2005, Aguilar et al. 2000).

Respiratory specimens are usually collected from the upper respiratory tract rather than from the infection site (lower respiratory tract) (Ruuskanen et al. 2011). Upper respiratory specimens, including nasopharyngeal aspirates, washes, and swabs are widely used in pneumonia aetiological studies. A nasopharyngeal aspirate is generally considered the specimen of choice for paediatric patients as it gathers both nasal and nasopharyngeal mucus samples. The use of PCR–based tests in combination with nasal–throat swab can yield a diagnosis with similar sensitivities to the nasopharyngeal aspirate for IFV, hMPV, and hPIV (Do et al. 2011, Lambert et al. 2008). A comparison between nasopharyngeal swab (NPS) and oropharyngeal swab (OPS) did not yield a consistent result for the three viruses (Kim et al. 2011). The OPS was more

sensitive for influenza B, hPIV–2, and hPIV–3, while less sensitive for influenza A and A/H1N1pdm09; the two specimens did not differ significantly for hMPV and hPIV–1. Lower airway specimens, including sputum, transtracheal aspirate, bronchoalveolar lavage, and lung puncture, have the advantage for establishing a diagnosis because they are from the infection site. However, there are some potential problems with lower respiratory specimens, such as the contamination of these specimens and safety issues (Ruuskanen et al. 2011, Turner et al. 2012, Hammitt et al. 2012).

1.7. Co–infections and super–infections

Viral co–infections are common in children, while the clinical significance of viral co–infections is unclear. The association between viral co–infections and disease severity is unclear. Viral co–infections are not associated with increased severity of respiratory infections according to one systematic review of children under 18 years with ARI (Scotta et al. 2016). In contrast, viral co–infections might increase the mortality risk among children hospitalised with ARI as revealed from another systematic review; this finding, however, was based on only one study with a high risk of bias (Asner et al. 2014).

The interaction of viruses and bacteria has been explored in different types of studies. These studies include animal models, time–series analyses investigating the temporal association between viral and bacterial infections, and clinical trials assessing the impact of pneumococcal conjugate vaccine on viral respiratory hospitalisations in children (Lee et al. 2016, McCullers 2014, Kukavica-Ibrulj et al. 2009, Madhi et al. 2006, Grijalva et al. 2014, Ampofo et al. 2008, Li et al. 2018, Madhi and Klugman 2004). Primary viral infections can increase the susceptibility of secondary bacterial infections through complex mechanisms at the host level, such as facilitating the adherence and invasion of bacteria and inhibiting host immunity, as well as lead to increased bacterial transmission at the population level (McCullers 2014, Mina and Klugman 2014).

Super–infections of bacteria, especially *Streptococcus pneumoniae*, can cause severe infections and even deaths (Mina and Klugman 2014, Seki et al. 2014, 2009, Madhi and Klugman 2004, Madhi et al. 2007, Madhi et al. 2006, Klugman et al. 2018, Simonsen et al. 2011).

1.8. Advantages and general issues of data on laboratory–confirmed viruses

Laboratory–confirmed data record the number of cases that are tested positive for viruses and are important data sources for burden estimation. However, several issues should be considered when analysing and interpreting the data. One case–control study of acute respiratory infection in Netherlands found that respiratory viruses were detected in 19% of people without respiratory symptoms, and no viruses were detected in 50% of people with acute respiratory infections (van Gageldonk-Lafeber et al. 2005). This finding highlights several issues related to analysing and interpreting data on laboratory – confirmed viruses. First, the carriage of pathogens in the upper respiratory tract is common in healthy children or in children with mild upper respiratory infections, and it is challenging to establish the causality between the pathogen identified in the upper respiratory specimens and ALRI. As revealed from recent prospective multi–country ALRI case–control studies and a systematic review, the presence of IFV, hPIV, and hMPV in upper respiratory specimens was significantly associated with ALRI hospitalisation among children under five years (Shi et al. 2015, Benet et al. 2017, Pneumonia Etiology Research for Child Health Study Group (PERCH) 2019). Results from recent pooled analyses suggested that 80–98% and 73–91% of hospitalised IFV– and hMPV–positive ALRI cases could be attributed to the two viruses at the population level; the aetiological fraction could vary by hPIV serotypes, with 87% for hPIV–1, 62–85% for hPIV–3, 43–62% for hPIV–4, unclear for hPIV–2 (Shi et al. 2015, Benet et al. 2017, Pneumonia Etiology Research for Child Health Study Group (PERCH)

2019). Second, the aetiological fraction of each virus is complicated by the presence of multiple agents in a specimen. It is hypothesized that some agents may be bystander and innocent, while others are the causative pathogens (Shi et al. 2015). Consistent with this hypothesis, results from the two multi–country pneumonia case–control studies showed that the associations between pneumonia and IFV, hMPV, and hPIV appeared to be stronger after adjusting for the presence of other agents (viruses and bacteria), with one exception for hPIV–2 (Benet et al. 2017, Pneumonia Etiology Research for Child Health Study Group (PERCH) 2019). The results reaffirm that the three viruses are important causative pathogens of childhood ALRI. Third, the patients in whom no pathogen is identified may be caused by some pathogens that are difficult to detect, other pathogens that have not been studied, or pathogens that are missed (Woodhead 2002). A virus can cause infections while remain not detected for some reasons. For example, a virus can be undetectable due to the late collection of specimens, the inappropriate quality of specimens, and the poor sensitivity of a test method. Additionally, certain viruses, influenza virus for example, can expose individuals to secondary bacterial infections; the virus may stop shedding and cannot be detected when children receive care. Consistent with this, results from trials assessing maternal influenza immunisation reveal that influenza is responsible for about 20% of hospitalised ALRI in infants under six months, which is much higher than the estimates using laboratory–confirmed data (Nunes et al. 2017, Omer et al. 2018). Despite the advantage of using vaccine probe studies to quantify both direct and indirect role of a virus in causing ALRI, the conduct of these studies relies on the presence of vaccines targeting a virus. Burden estimation using vaccine probe studies are only feasible for certain pathogens, for which targeted vaccines exist. For other pathogens, traditional or emerging ones, burden estimates reply on laboratory–confirmed data and/or statistical models.

1.9. Overview of approaches and models used to estimate global burden of viral respiratory infections

Laboratory–confirmed viral ALRI incidence rate and case–fatality ratio are simple and straightforward statistics to derive viral ALRI morbidity and mortality burden. Laboratory–confirmed data are mainly from health facilities and are very limited in community settings. This is because specimen collection and laboratory diagnostic test is rarely performed if patients do not seek care or only seek care at certain informal care providers, such as private pharmacies, except for in very limited areas where aetiology studies are ongoing to identify cases through household visits. Even in health facilities, not all patients with respiratory symptoms are sampled and tested, especially deaths (Feikin et al. 2017). There are some reasons for the under–detection and under–representation of deaths in aetiology studies. Some critically ill children die prior to specimen collection. Moreover, critically ill children are usually not enrolled or sampled in aetiology studies because of parents' refusal and the urgent need for treatment. In light of the challenge in systematically identifying and diagnosing infections, especially deaths, several statistical models have been developed. Table 1–1 summarises the details of models that commonly used in the estimation of global viral respiratory mortality.

Table 1-1. Approaches and models commonly used to estimate the global mortality of virus–associated ALRI or virus–attributable ALRI.

	Population attribution fraction of a virus AND relative case–fatality ratio (CFR) multiplier model	In–hospital mortality AND care-seeking multiplier ("inflation factor") model	Regression analysis AND respiratory mortality multiplier model	Regression analysis AMD mortality risk factor model
Key reference	(Troeger et al. 2019)	(Nair et al. 2011, Shi et al. 2017)	(Iuliano et al. 2018)	(Simonsen et al. 2013)
Input data	(1) The number of ALRI deaths. (2) The percent positivity of a virus (e.g., IFV). (3) The attributable fraction for a virus. (4) The relative CFR of a virus versus other pathogens. In the key reference, the study used the relative CFR of viral ALRI versus bacterial ALRI.	(1) In–hospital mortality: i. Virus–associated ALRI hospitalisations. ii. CFR for a virus. (2) Overall virus–associated mortality using a simple regression model: i. Monthly number of pneumonia deaths over consecutive years. ii. Defined seasonality for a virus.	(1) Country–specific respiratory mortality rates. Using regression models on: (2) Weekly or monthly number of respiratory deaths over consecutive years. (3) Concurrent viral activity data.	Using regression models on: (1) Weekly or monthly number of respiratory deaths. (2) Concurrent viral activity data. (3) Country indicators.
Setting	(1) Mortality data from mixed settings (hospital and community settings) (2) Estimates of attributable fraction, percent positivity, and CFR are mainly from hospital settings.	(1) Pneumonia death data from mixed settings. (2) Virus' seasonality data from mixed settings (inpatient and outpatient departments)	Respiratory mortality data and virus activity data from mixed settings.	Mortality data and virus activity data from mixed settings.

	Population attribution fraction of a virus AND relative case–fatality ratio (CFR) multiplier model	In–hospital mortality AND care-seeking multiplier ("inflation factor") model	Regression analysis AND respiratory mortality multiplier model	Regression analysis AMD mortality risk factor model
Key assumptions and limitations	(1) Limited data by time points and / or locations and limited representativeness of input data. (2) Not all cases and deaths are tested, and testing practice varies between sites. Fatal cases are less likely to be sampled and tested. (3) One assumption is that the relative CFR estimate, which are obtained from hospital settings, can be generalizable to community settings. (4) Estimates can be affected by the quality of data on mortality and cause of death. (5) This key reference used a splitting strategy to attribute total deaths to each cause, so the mortality for a virus relied on the splitting process.	⬅ See (1) to (2) for the first model. (3) No deaths are attributed to a virus outside seasons. All excess pneumonia deaths in seasons are attributed to the virus. (4) The association between deaths and the seasonality of virus might be confounded by other factors. (5) For a given country, the inflation factor was calculated using an average in-hospital mortality (e.g., in developing countries) rather than the estimate for the country. Thus, in addition to care–seeking, inflation factor can be associated with country child mortality rates. (6) The regression analysis may be inapplicable in tropical areas where the seasonality of certain virus (e.g., IFV) is less defined.	⬅See (1) to (2) for the first model. (3) The number of deaths associated with a virus is temporally related to the activity of a virus and subtypes though a year. (4) The variation in the reported virus activity over time accurately reflects the changes in the activity of a virus, or in other words, the testing practice remains stable over a year. (5) The key reference used a key assumption that the respiratory mortality rate differences between countries reflected the differences in virus activity and the risk of virus–respiratory deaths between countries. Based on this assumption, rates of virus–respiratory death were imputed for countries without input data for the temporal regression analysis (i.e., virus activity data and respiratory death data). (6) Because of using national death data, estimates can be affected by the quality of data on mortality and cause of death. (7) The regression analysis may be inapplicable in tropical areas where the seasonality of certain virus (e.g.	⬅See (1) to (2) for the first model. (3) to (4) similar to "respiratory mortality multiplier model". (5) The key reference used the statistical correlations between country–specific influenza–associated mortality and country indicators to impute data for countries (e.g., African countries) without input data for the temporal regression analysis. The modelled statistical correlations may not be generalizable to no–data countries. (6) Because of using national death data, estimates can be affected by the quality of data on mortality and cause of death. (7) The regression analysis may be inapplicable in tropical areas where the seasonality of certain virus (e.g., IFV) is less defined.

	Population attribution fraction of a virus AND relative case–fatality ratio (CFR) multiplier model	In–hospital mortality AND care-seeking multiplier ("inflation factor") model	Regression analysis AND respiratory mortality multiplier model	Regression analysis AMD mortality risk factor model
Advantages	(1) Proportion data are more available than incidence data. (2) This model is developed to yield country–specific estimates.	(1) Compared with the first model, CFR data, which are mainly available in hospital settings, are only used to yield the mortality estimate in hospital settings. (2) The use of a regression model may account for the deaths for which a viral diagnosis is missing, or a given virus is undetectable but is associated with the outcome. (2) The whole model does not yield country-specific estimates.	(1) The use of a regression model may account for the deaths for which a viral diagnosis is missing, or a given virus is undetectable but is associated with the outcome. (2) This model is developed to give country-specific estimates.	(1) The use of a regression model may account for the deaths for which a viral diagnosis is missing, or a given virus is undetectable but is associated with the outcome. (2) This model is developed to yield country-specific estimates.

1.10. Conclusion

Reducing mortality among children under five years is prioritised in Sustainable Development Goals, and the reduction needs to be accelerated to achieve the Sustainable Development Goals by 2030 (United Nations 2019, Boerma et al. 2018, WHO 2005b). As one of the leading causes of deaths, ALRI mortality among children under five years has substantially decreased over the past 10 years; continued progress will partly rely on targeted prevention and treatment against leading pathogens in the future. This work focused on ALRI burden associated with IFV, hMPV, and hPIV as the three viruses are three leading causative pathogens of ALRI in children under five years. Despite the causative roles, the global burden estimates for hMPV–associated and hPIV–associated ALRI are unavailable, and there are no licenced vaccines or approved antiviral treatments for the infections. New global and regional estimates are of important value in generating an overview of the impact of a particular virus. Regular and timely updates allow for the assessment of emerging trends, progress, and intervention effectiveness; particularly for IFV, regular updates can provide evidence to improve pandemic influenza response. Both new and regular updated estimates can help guide health investment priorities and resource allocation (Boerma and Mathers 2015).

Unlike hMPV and hPIV, IFV has been the focus of studies for years. Nair and colleagues (Nair et al. 2011) previously estimated that IFV was associated with 20 million cases of ALRI, one million cases of severe ALRI, and 28,000–111,000 ALRI deaths in children under five years in 2008. After this study, three studies have estimated global burden of IFV–associated or IFV–attributable ALRI in children under five years using different approaches. The approaches are summarised in Table 1–1. Results from two of the three studies suggested that IFV was associated with 870,000 ALRI hospitalisations, and 45,000 ALRI deaths in children under five years during 2012–2015 (Lafond et al. 2016, Iuliano et al. 2018). The third study estimated about 8 million ALRI cases, 2.2 million ALRI hospitalisations, and 23,400

ALRI deaths were attributed to IFV in children under five years in 2017 (Troeger et al. 2019). The difference in these estimates in part reflects the difference in the methodology between studies.

One major advantage of the current report is the inclusion and analysis of laboratory–confirmed viral ALRI burden data, such as incidence rates, hospitalisation rates, and case–fatality ratios. Published data are either very limited in low– and middle–income countries, or mostly provide estimates for broad age groups, especially for case–fatality ratios. However, burden for finer age groups is of great relevance to the development of related policies and prevention and treatment strategies. The understanding of the challenge in data availability in published literature and the importance of the global burden estimates has led to important collaborations, allowing for improvement in methods and estimates. The Respiratory Virus Global Epidemiology Network, as a collaborative network on respiratory viral infections, has contributed data by finer age groups and years from different geographic locations, especially from low– and middle–income countries experiencing high childhood ALRI burden. In combination with the data, the incidence rate–based approach and the case–fatality ratio multiplier approach were used in the current analysis to derive the global burden of the three viruses. Incidence rates can be seen as the combination of two matched estimates from the same population: the incidence rate of total ALRI and the proportion of a given virus in total ALRI. In contrast, using the proportion–based approach, proportion estimates and ALRI burden estimates from different locations and time points are usually combined. Thus, the proportion–based approach requires an additional assumption that proportion data are generalizable to populations where the ALRI burden estimates are from, which the incidence–based approach does not require.

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Chapter 2 Objective

The overall objective for this report is to estimate the global burden of IFV–associated, hMPV–associated, and hPIV–associated ALRI in children under five years. The specific objectives are as follows.

1. To estimate the incidence rate and the number of IFV–associated, hMPV–associated and hPIV–associated ALRI cases in the community setting;

2. For IFV, to additionally estimate the burden of the whole spectrum of respiratory infections (i.e., including mild respiratory infections, severe infections, and deaths due to respiratory infections) associated with IFV in the community setting.

3. To estimate the hospitalisation rate and hospitalisations of IFV–associated, hMPV–associated, and hPIV–associated ALRI.

4. For hMPV and hPIV, to additionally estimate the proportion of hMPV and hPIV in hospitalised ALRI cases, and use these as input data for a proportion–based approach to estimate the hospitalisations of hMPV–associated and hPIV–associated ALRI.

5. To estimate hospitalised case–fatality ratios (hCFRs) due to IFV–associated, hMPV–associated, and hPIV–associated ALRI.

6. To estimate the in-hospital mortality and the overall mortality (including both deaths occurring in hospitals and out of hospitals) due to IFV–associated, hMPV–associated, and hPIV–associated ALRI.

7. Where available, to estimate the hospitalisation rate and the hospitalisations of IFV–associated, hMPV–associated, and hPIV–associated ALRI cases with hypoxaemia and any danger signs, or requiring ICU admission or mechanical ventilation.

Chapter 3 Standardised methods

A standardised methodology and process was followed to estimate the burden of IFV, hMPV, and hPIV, from the conduct of the systematic literature review, identification and assembly of high–quality unpublished data, use of standardised case definitions, risk of bias assessment tool to the statistical analysis. The standardised part of the methodology is presented in this chapter. The term “virus” in this chapter is used to refer any of IFV, hMPV, or hPIV to simplify the expression. Any adaptations in the methodology for a particular virus, where applicable, are presented separately in the chapter for each virus (Chapter 4–6).

3.1. Data source

3.1.1. Systematic review

Search strategy

Systematic reviews were conducted for IFV–associated, hMPV–associated and hPIV–associated ALRI burden among children under five years. The following databases were searched: Medline (Ovid), Embase (Ovid), Global Health (Ovid: 1973 onwards), CINAHL, Web of Science, Global Health Library, and three Chinese literature databases – CNKI, Wanfang, and Chongqing VIP. Search strategies are in appendices (A2 and A3). To search the grey literature, the author additionally carried out broad searches for each virus through Google search. Since the literature searches were conducted separately, the timespan was slightly different, and the details are available in the chapter for each virus. No language or publication restrictions were applied. At least one additional reviewer did the systematic reviews for each virus according to PRISMA guidelines (Moher, 2009). The reviewers carried out the search, screened the titles and abstracts for eligibility, and extracted data independently. Studies in languages other than Chinese or English were translated into English using Google Translate. Disagreements were resolved by discussion or an additional reviewer.

Inclusion and exclusion criteria

(1) Studies were included if they

- reported any of the following data in children under five years:
  - incidence rates of ALRI and more severe infections with laboratory–confirmed virus (IFV, hMPV, or hPIV) in the community;
  - hospitalisation rates of ALRI and more severe infections with laboratory–confirmed virus (IFV, hMPV, or hPIV);
  - hospitalised case–fatality ratios (hCFRs) of ALRI with laboratory–confirmed virus (IFV, hMPV, or hPIV);
  - the proportion of a virus (hMPV or hPIV) in hospitalised ALRI cases.
- AND reported data for at least one complete calendar year, or at least one full season for a particular virus in temperate climate regions; applicable only to incidence and hospitalisation rates. The hCFR data for any length of period were included. For proportion data, only data for complete calendar years were included.

- AND used a clearly defined case definition for specimen collection and testing.

(2) The reviewer excluded studies

- without a clear denominator (limited to the incidence and hospitalisation rate data). Both denominator and numerator are required as input data of the meta–analysis.
- in which a virus was not the primary outcome. In detail, studies were excluded if they only reported the cases tested negative for other pathogens, potentially excluding the co–infections between the studied virus and other pathogens. Studies were also excluded if they only

reported the co–infections between the studied virus and other pathogens.

- in which the morbidity and mortality estimates were derived from modelling techniques (e.g., regression analysis).
- in which infections were diagnosed based on serology alone. The author determined to exclude studies using serological testing alone because it has a very strict requirement on the timing of specimen collection (paired acute–phase and convalescent–phase serum specimens). Patients can seek care a few days after the disease onset, and the acute–phase antibodies may have increased at the time of specimen collection. In the case, serology yields results with poor sensitivity among young children (Sawatwong et al. 2012).
- Only reporting nosocomial infections.
- Only including population subgroups with high–risk conditions (e.g., chronic underlying diseases).

Identification of unpublished data

The Respiratory Virus Global Epidemiology Network has been established and has contributed data to the development of global burden estimates of ALRI and key respiratory viruses in children under five years, such as global burden of ALRI due to respiratory syncytial virus (2010/2015) and seasonal influenza virus (2008), and global hospital admissions for severe ALRI (2010) (Nair et al. 2013, Nair et al. 2011, Shi et al. 2017, Nair et al. 2010). Since 2015 this collaboration network has included more than 70 investigator groups working on respiratory viral infections and provided high–quality unpublished data to supplement the systematic review (Shi et al. 2017). Standardised case definitions were formulated within the network, and data were shared through standardised approaches (standardised data collection templates and case definitions) to data analysis. Other investigators with relevant data were also invited to contribute data and participate in the

analysis. The standardised case definitions are in appendices (A4). Generally, unpublished data from the collaboration network had a low risk of bias in case definition and test method compared with data from published literature due to the recommended use of the standardised case definition and the use of molecular tests. Data shared by the collaboration network were also checked using the eligibility criteria.

3.2. Definitions

A “study” was defined as a dataset at one site in one published paper or from one research group in the collaboration network. Studies were classified by case ascertainment:

- Community–based studies with active case ascertainment: studies where the cases are actively identified and their respiratory specimens are collected through regular visits to households. Studies conducted in primary care facilities (e.g., outpatient departments or the offices of general practitioner) in high–income countries with good access to care are also considered as good proxies of community–based studies.

- Hospital–based studies with passive case ascertainment: studies where the cases are identified when they are admitted into hospitals.

We used separate standardised case definitions for community–based studies and hospital–based studies (Appendix A4) (Shi et al. 2017). For community–based studies, the 2005 WHO Integrated Management of Childhood Illnesses (IMCI) case definition for clinical pneumonia was used to define ALRI because this definition has been widely employed in most community–based studies, and has been widely used as an indication of the treatment of pneumonia (WHO 2005a). There are another two severity levels for community–based studies: (1) severe ALRI, defined as ALRI with chest wall indrawing; (2) very severe ALRI, defined as ALRI with any general danger signs according to 2005 WHO IMIC definition (WHO 2005a). For

hospital–based studies, hospitalised ALRI was defined as the physician diagnosed ALRI who required or was recommended hospitalisation because the diagnoses mostly depend on physicians' clinical judgement. There are another two severity levels for hospital–based studies: (1) ALRI with hypoxaemia; (2) very severe ALRI cases, defined as hospitalised ALRI with any general danger signs according to 2005 WHO IMCI definition (WHO 2005a), admitted into intensive care units (ICUs), or requiring mechanical ventilation (MV). The relationship between outcomes is shown in the figures below. In brief, the strata of less severe cases include the strata of more severe cases.

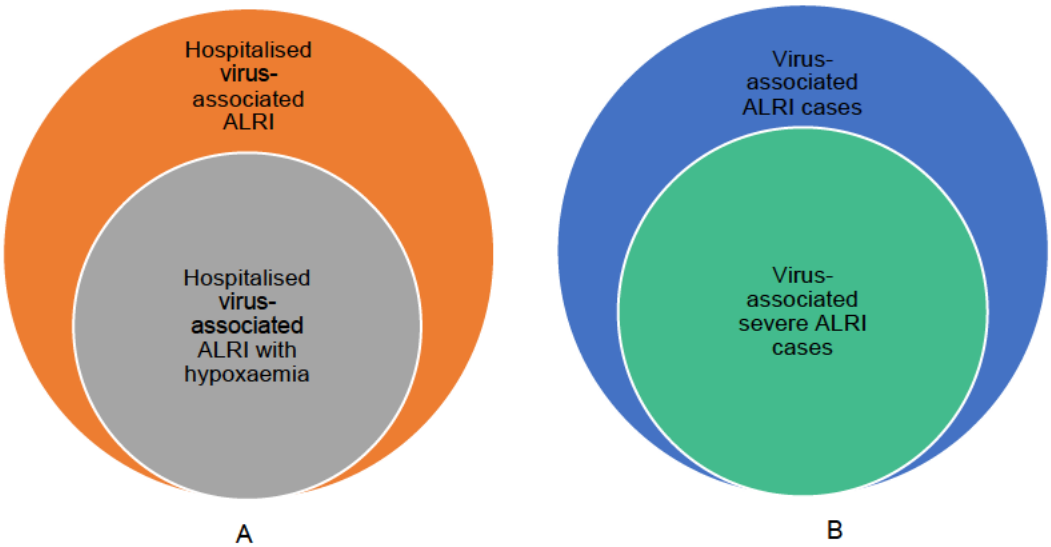

Figure 3-1. Relationship between outcomes.

A: hospitalised virus–associated ALRI and virus–associated ALRI with hypoxaemia. B: the relationship between community virus–associated ALRI and virus–associated severe ALRI. The size of each circle is not proportional to the number of cases for each severity.

3.3. Assessment of bias

The Newcastle–Ottawa Scale was specifically modified to assess the risk of bias of individual studies in this work. The newly modified scale contains seven domains – study design, adjustment for health utilization, patient groups excluded, case definition, sampling strategy (i.e., how cases were selected for sample collection and testing), diagnostic test method, and hypoxaemia ascertainment. The details of the assessment tool are given in Appendix A5. Critical assessments on the risk of bias (high and low) were made separately for each domain. Of these domains, sampling strategy (different levels of testing) were taken into account in meta–analyses of incidence rates and hospitalisation rates. Details will be provided in the section of Statistical analysis. Other domains were not taken into account in meta–analyses because it was difficult to quantify the extent of the bias and to have a valid weighting strategy.

3.4. Statistical analysis

Generally, standardised analysis (e.g., data preparation and analysis) was conducted for IFV, hMPV, and hPIV, with certain adaptations for each virus due to the difference in data availability. The part of standardised analysis is presented in this chapter, and any adaptation is presented in Chapter 4–6. A simplified process for the burden estimation is presented in Figure 3–2. All analyses were done in R version 3.5.2, particularly the metafor package (R Core Team 2018, Viechtbauer 2010). The characteristics of individual studies were summarised and are available in the Appendix (A19). Results from sensitivity analysis are available in the Appendix (A8–12, 14, 16).

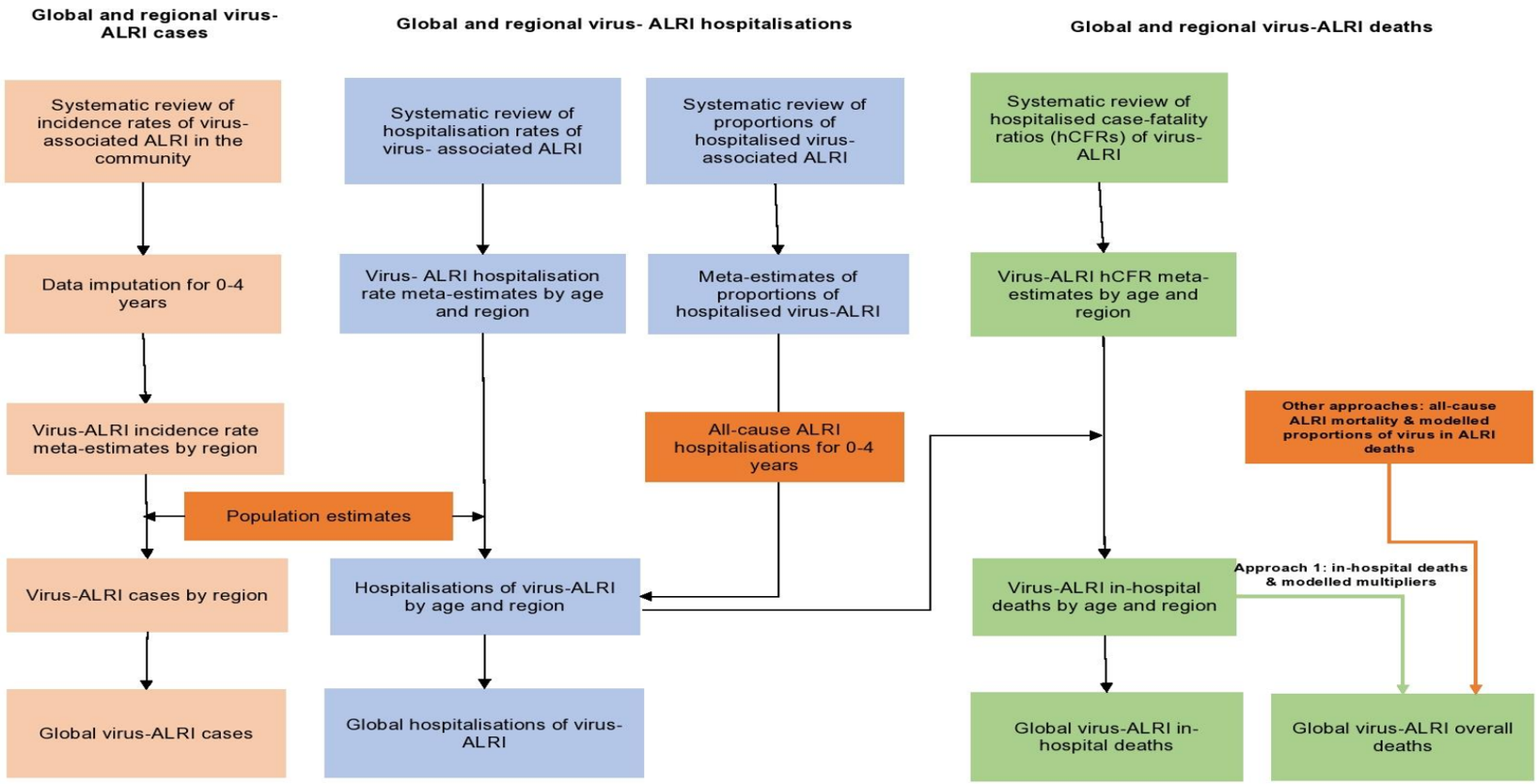

Figure 3-2. A schematic figure showing the process to estimate global burden of virus–associated ALRI in children under five years.

"Virus" denotes any of influenza virus, human metapneumovirus, and human parainfluenza virus. This figure summarises the approach for each outcome, and shows how they relate to each other. Global hospitalisations for virus–ALRI were estimated by applying virus–ALRI hospitalisation rates to population estimates. Virus–ALRI in–hospital deaths were developed on hCFRs of virus–ALRI and the virus–ALRI hospitalisations. The overall mortality of virus–associated ALRI was modelled through two routes: (1) applying a multiplier ("inflation factor") to the in–hospital mortality; (2) applying the percent of a virus in ALRI deaths to total ALRI mortality. Different approaches and data were utilised to yield the results in the two routes. ALRI: acute lower respiratory infection. hCFR: hospitalised case–fatality ratio.

3.4.1. Data preparation

Data validation and exclusion of duplicate records

A consistency check was performed for unpublished data using information in the standardised data collection template. For example, the subtype cases (or deaths) should add up to the number of virus–confirmed cases (or deaths) unless there are co–infections between subtypes. The reported annual percent of virus–confirmed ALRI cases should match with the monthly counts of ALRI cases and tested cases. A plausibility check was performed on the number of cases between severity levels; by definition, the number of cases in the less severe outcome strata should be greater than the number of cases in the more severe outcome strata, as the more severe strata is a subset of the less severe strata. For example, the number of hospitalised ALRI cases should be greater than the number of hospitalised ALRI cases with hypoxaemia. Any issues were resolved through discussion with researchers from individual sites who had compiled the data.

Duplicate data were defined as multiple datasets from an identical group of population (e.g., in the sense of age, location, time). The procedure to deal with duplicate data was to include either the more detailed dataset (e.g., stratified by finer age groups) or the more recent version.

Data scaling

Not all the eligible cases (e.g., children with ALRI symptom) were sampled or tested. To avoid underestimation caused by the under–detection, a commonly used method is to scale the case number (numerator) when estimating incidence and hospitalisation rates for a certain virus. The adjusted case number is equal to the observed case number dividing by the proportion of tested cases (Formula 3–1). In this thesis, however, the population at risk (denominator) was scaled based on levels of testing, and the adjusted denominator and the

observed case number was the input data of the meta-analysis (Formula 3–2). Data were not adjusted when data on levels of testing was unavailable. The rates derived from the two formula are the same. Formula 3–2 was chosen in this thesis because compared with the original denominator, the scaled denominator better reflects the size of study sample and the precision of each study.

Formula 3–1 – scaling the case number:

$$\text{Rate} = (\text{No. of observed cases}/\text{Proportion of testing})/\text{Original denominator}$$

Formula 3–2 – scaling the denominator (used in this thesis):

$$\text{Rate} = \text{No. of observed cases}/(\text{Proportion of testing} * \text{Original denominator})$$

Using Formula 3–1, the original denominator would be the input data of meta–analysis, while in Formula 3–2, the scaled denominator would be the input data.

Proportion data or hCFR data were not adjusted. The input data for the analysis of proportion were the number of tested cases and the number of laboratory – confirmed cases; for hCFR, the input data were the number of laboratory-confirmed cases and laboratory-confirmed deaths.

3.4.2. The selected age bands and the rationale

Previous studies suggest that infants aged 0–5 months and 6–11 months tend to have higher hospitalisation rates and hCFRs of ALRI compared with children aged 12–59 months(Nair et al. 2013, Shi et al. 2017), so one of the priorities of this work was to estimate burden stratified by three narrow age bands – 0–5, 6–11, and 12–59 months. However, for certain outcome it is challenging to perform age – stratified analyses due to the lack of data by age groups. In this scenario, imputation was performed to allow inclusion of data from as many studies as possible and avoid loss of information.

3.4.3. Data imputation

To follow up and expand the preceding paragraph, it is challenging to estimate incidence rates by age group in the community because there are very limited data, especially age–stratified data, in this setting. Therefore, it was determined to analyse and report estimates for 0–59 months as an overall age group (not stratified by age) in the community. Several studies reported data for 0–11 months, 0–23 months, and 0–35 months; to incorporate the information from these studies, the missing incidence rate for 0–59 months was imputed based on the available data in these age groups.

The imputation was done at the study level following three steps: (1) imputing the denominator; (2) imputing the rate; (3) calculating the case number using the denominator and rate. The step (2) and (3) were skipped if the case number was available. The reference group referred to the age group with available rate data and could be one of 0–35 months, 0–23 months, and 0–11 months. When two or more age groups were available, the reference group was chosen in the following order: 0–35 months, 0–23 months, to 0–11 months.

Details of each step of imputation were:

- The denominator was imputed by country income regions based on the probability of dying between age n and n+x ($_nq_x$) for both sexes in 2013, obtained from WHO life tables (World Health Organization, 2017). The proportion of total under–five population that are in the reference age group was calculated using the $_nq_x$ estimates (World Health Organization, 2017). Using this proportion and the denominator in the reference group, the denominator for 0–59 months was estimated. Since the $_nq_x$ is only available for 0–11 months and 12–59 months, one assumption is that the probability of dying is the same from 12 to 59 months (this assumption is only required when using 0–23 months and 0–35 months as the reference group). Another assumption is that the structure of population

under five years for each site is similar to the population structure for the corresponding country income region.

- The case number was imputed using a multiple imputation approach assuming the rates for 0–59 months were missing at random (Sterne et al. 2009). Figure 3–3 shows the process. First, meta–analysis was performed to estimate the rate ratios between 0–59 months and any of 0–11 m, 0–23 m, and 0–35 m (meta–analysis was only done when there were three or more studies). Second, the pooled rate ratio was assumed to follow a log–normal distribution, and 100 samples of rate ratios were simulated. Third, 100 samples of rates for 0–59 months were generated based on the rate in the reference group and the corresponding rate ratios. Fourth, case numbers were calculated using the denominator and imputed rates. Using the method, 100 datasets of imputed case numbers were generated. Fifth, meta–analysis was done for each dataset, and the meta–estimates were combined together using the Rubin's rules (Rubin 1987, Honaker et al. 2011).

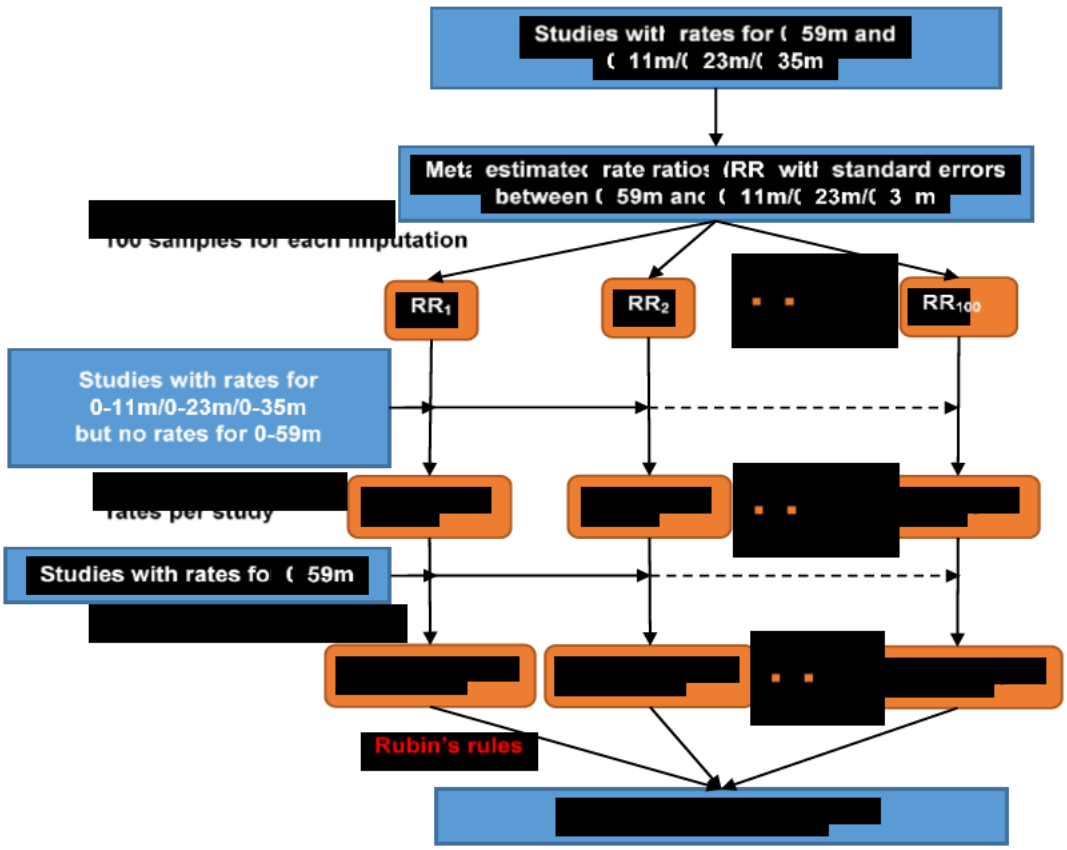

Figure 3-3. Imputing missing rates for 0–59 months using the multiple imputation approach.

In the previous analysis for IFV, missing rates were imputed based on median rate ratios between 0–59 m and any of 0-11 m, 0-23 m, and 0-35 m (Nair et al., 2011). Different from the multiple imputation approach, there was one fixed imputed rate and case number for one study. Estimates from the multiple imputation approach were compared with those from the median rate ratio approach (Appendix A6).

3.4.4. Meta–analysis

3.4.5. **For each outcome, the numerator and the denominator were extracted from individual studies as they were reported, or were calculated using available data. In light of the differences in methodology (e.g., the adjustment of healthcare utilisation, case definition, sampling strategy, test methods), population epidemiology (e.g., child health condition), access to care and case management between studies, heterogeneity between studies was anticipated for each outcome, and a generalised linear mixed model was used to estimate the incidence rates, hospitalisation rates, proportions, and hCFRs of virus–associated ALRI. Compared with the classic random–effect model, this model has an advantage in analysing small studies and studies with few events, and does not require adding a continuity correction in case of zero events (Stijnen et al. 2010). Estimates from the generalised linear mixed model were compared with the estimates from the classic random–effect model (Appendix A8). Similar to the classic random–effect model, the generalised linear mixed model assumes that the observed estimates can vary between studies due to the differences in epidemiology and sampling variability (within–study error) (Riley et al. 2011). Thus, for each study the observed effect is sampled from a distribution of the true effect, and different studies are assumed to have different true effects, which all follow a distribution. Based on this general concept, the generalised linear mixed model accounts for two levels of variance – within studies and between studies. The model decomposes the observed variance into within–studies and between–studies variance and uses them to assign weights to different studies. Since the within–study variance depends on the study sizes, a larger study would be given to a relatively larger weight compared to a smaller study. In this way, the model generates a weighted average estimate across all studies. Since the study sizes were scaled based on the levels of testing in the meta–analysis of incidence rates and**

hospitalisation rates, so the model takes account of differences in testing practice between studies. No other covariant was added in the meta–analysis. Stratified analyses were conducted by age groups and region groups. Some studies reported data for multiple sites, and potential dependency between the estimates from these sites might exist due to the use of similar methods. However, the limited number of studies and precision do not allow for the use of hierarchical analyses (e.g., three–level meta–analyses). Morbidity estimation

Virus–associated morbidity burden

To estimate the number of virus–associated ALRI cases and hospitalisations, the incidence rates and hospitalisation rates of virus–associated ALRI were applied to the population estimates. The population estimates for 2018 were used (United Nations et al. 2017). The burden and uncertainty range (UR) were estimated using the Monte Carlo simulation (Shi et al. 2017). In detail, the pooled incidence rates and hospitalisation rates from the meta-analysis were assumed to follow log–normal distributions. A set of 10,000 samples was simulated from the mean and standard error, and was multiplied by the population estimates to yield a new set of samples, which approximated the distribution of the number of cases and hospitalisations. The median value of the 10,000 samples and the 2.5th and 97.5th percentiles were extracted as the point estimate and the 95% UR.

Stratified analysis was conducted by three non–overlapping age bands (0–5 months, 6–11 months, and 12–59 months) and by 2018 child mortality settings (low; high: the median value of under–five mortality rate as the cut–off point) for each outcome where available (United Nations Inter-agency Group for Child Mortality Estimation 2019). Attempts have been made to stratify data into four child mortality settings based on the quantile of country under–five mortality rates. But due to the limited number of studies in each age– and region–strata, it was determined to classify data into two groups.

For the community setting, the incidence rate for 0–59 months was estimated due to the small number of studies as mentioned earlier. Data were also stratified by country development status according to UNICEF definitions, World Bank income regions [low–income countries (LICs), lower–middle income countries (LMICs), upper–middle income countries (UMICs), and high–income countries (HICs)] (The World Bank). Due to the small number of studies in LICs, the LICs and LMICs were combined (as LMICs) when reporting estimates. Global results are the sum of age– and region–specific estimates. The numbers of cases were rounded to the nearest thousand.

Virus–attributable morbidity burden

As mentioned in the background chapter, the detection of a virus in upper respiratory specimens does not mean a causal relationship between the virus and the condition (i.e., ALRI). The attributable morbidity burden was estimated by combining the virus-associated burden estimates and the corresponding attributable fraction (AF). The AFs for virus–associated ALRI cases were calculated using data from one systematic review and two recent multi–country pneumonia case–control studies in children under five years (Shi et al. 2015, Pneumonia Etiology Research for Child Health Study Group (PERCH) 2019, Benet et al. 2017) .

Sensitivity analysis

As mentioned earlier, the global burden estimate was summed by child mortality settings as specified a priori in the main analysis. Other strata, such as World Bank income regions and country development status, are also commonly used when extrapolating available data to countries and regions without data. These stratifications, especially World Bank income regions, are relevant to the development and implementation of prevention and treatment strategy and resource allocation. The morbidity burden for each virus was also estimated and reported by these strata. Global burden estimates aggregated by these strata were reported in the sensitivity analysis, and were compared with the estimates from the main analysis.

Changes were considered non-noticeable if the 95% URs of global burden estimates completely overlapped, or if the change in the point values was 10% or less.

Moreover, available multi–year data were checked to assess how the incidence or hospitalisation rates of virus–associated ALRI had changed over years and to observe the variation between years. All studies with virus–ALRI incidence or hospitalisation rates over more than five consecutive years or seasons were eligible for this analysis. The yearly data, which were collected using the same methodology at the same geographical location throughout, were plotted by studies.

Potentially influential studies were examined using studentised deleted residuals, DFFITS, and Cook's distance (Viechtbauer and Cheung 2010). As summarised in the methodological paper, if the exclusion of a study leads to considerable changes in the fitted model, then the study is considered to be influential. The goal of this procedure was not to identify the "real" outliers, but to examine whether the meta–estimates were dependent on several potentially unusual studies (Viechtbauer and Cheung 2010). Any identified studies were compared with other studies among similar populations (e.g., the same or neighbouring locations) where available. The characteristics that might explain the "different" estimates were explored qualitatively.

3.4.6. Virus–associated mortality estimation

In–hospital mortality estimation

The in–hospital deaths of virus–associated ALRI were estimated by combining the virus–ALRI hospitalisations and hCFR meta–estimates using Monte Carlo simulation (Shi et al. 2017). First, a set of 10,000 samples approximating the distribution of hospitalisations was generated. Second, the pooled hCFR was assumed to follow log–normal distributions, and 10,000 samples for each hCFR was simulated from the mean and standard error. The samples of hCFR was applied to the 10,000 samples of hospitalisations

to yield a new set of 10,000 samples, approximating the distribution of in–hospital mortality.

Similar to morbidity burden, sensitivity analysis of mortality was conducted by different stratification scenarios. Moreover, available multi–year data were checked to assess how the hCFRs of virus–associated ALRI had changed over years. The numbers of deaths were rounded to the nearest hundred.

Overall mortality (in– and out–hospital mortality) estimation

(1) Main analysis

The overall virus–associated ALRI mortality can be classified into three broad groups: no hospital care seeking deaths, in–hospital deaths, and post–discharge deaths. The factor between the overall mortality and in–hospital mortality was defined as inflation factor in this thesis, as shown in Figure 3–5 (Nair et al. 2013, Shi et al. 2017). The inflation factor can be associated with many factors: the proportion of no–hospital–care–seeking deaths is associated with the access to care and care seeking behaviour; the proportion of post–discharge deaths is associated with malnutrition and HIV infections (Ngari et al. 2017, Chhibber et al. 2015, Chisti et al. 2014).

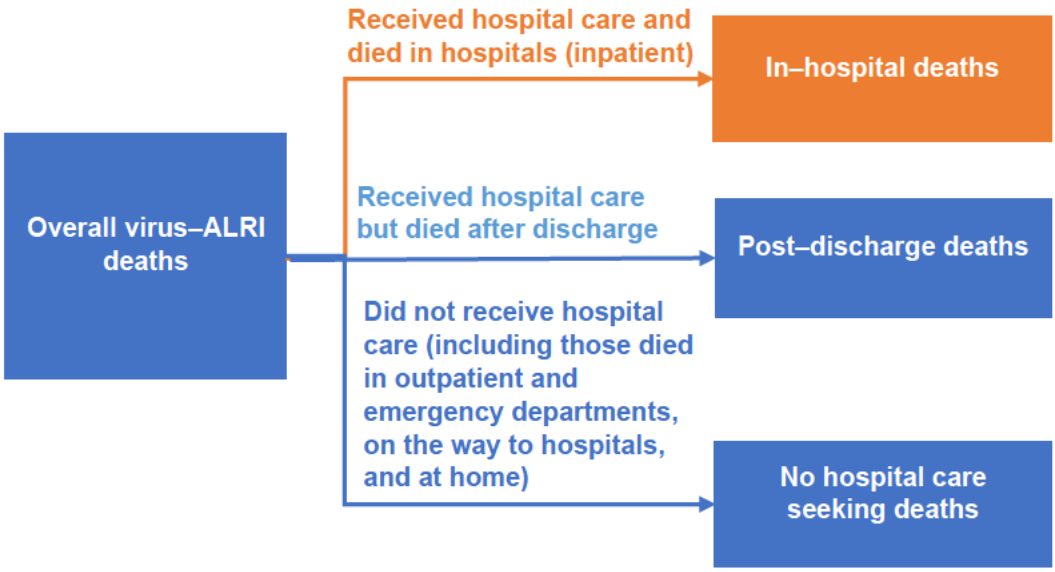

Figure 3-4. Broad groups of virus–associated ALRI mortality

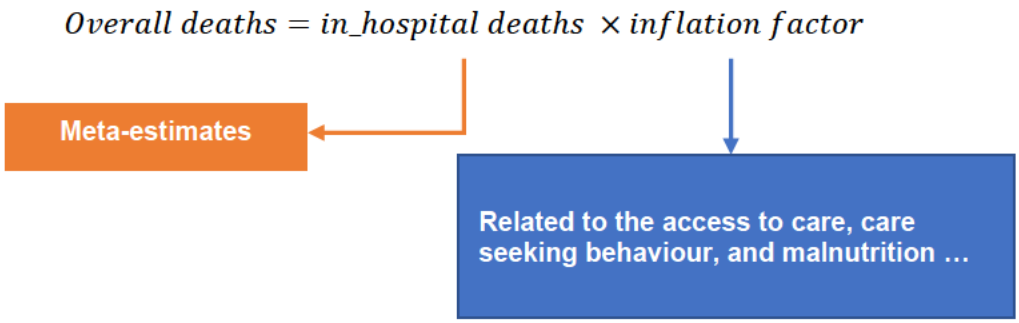

Figure 3-5. Relationship between virus–associated ALRI in–hospital mortality and overall mortality.

As shown in Figure 3–5, the in–hospital mortality was estimated using data from the systematic review (including published and unpublished data). Ideally the inflation factor for a virus should be estimated using the number of virus–confirmed deaths in hospital settings and in community settings. This is, however, almost impossible, because ALRI deaths are rarely tested in community settings. Since the inflation factor is associated with the care seeking, it can vary between different conditions (Bennett et al. 2015, Najnin et al. 2011, Onyango et al. 2012). So the best proxy for inflation factor of virus–confirmed ALRI deaths was considered to be the inflation factor of all–

cause ALRI deaths among children under five years. Next section is focused on the data source and estimation of the inflation factor and the virus–associated ALRI overall mortality.

(2) Main analysis – formula and data source

Figure 3–6 shows the estimation of the inflation factor and the virus–associated ALRI overall mortality. The data required in the analysis of the inflation factor are: (1) the number of total pneumonia deaths in children under five years among a defined population; (2) the number of deaths occurring in–hospitals among the same population. The eligible data were firstly obtained at six sites from the International Network for the Demographic Evaluation of Populations and their Health (INDEPTH) Network who had health and demographic surveillance data on defined populations; additional eligible data were obtained from two recently published studies (Sankoh and Byass 2012, Ferdous et al. 2018, Ahmed et al. 2018). Altogether, available data were from eight sites of six countries with high child mortality (Mozambique, Kenya, South Africa, Burkina Faso, Ghana, and Bangladesh). The median inflation factor was estimated using these data, and was applied to the in–hospital mortality in high child mortality settings to yield the overall mortality of virus–associated ALRI deaths in the setting.

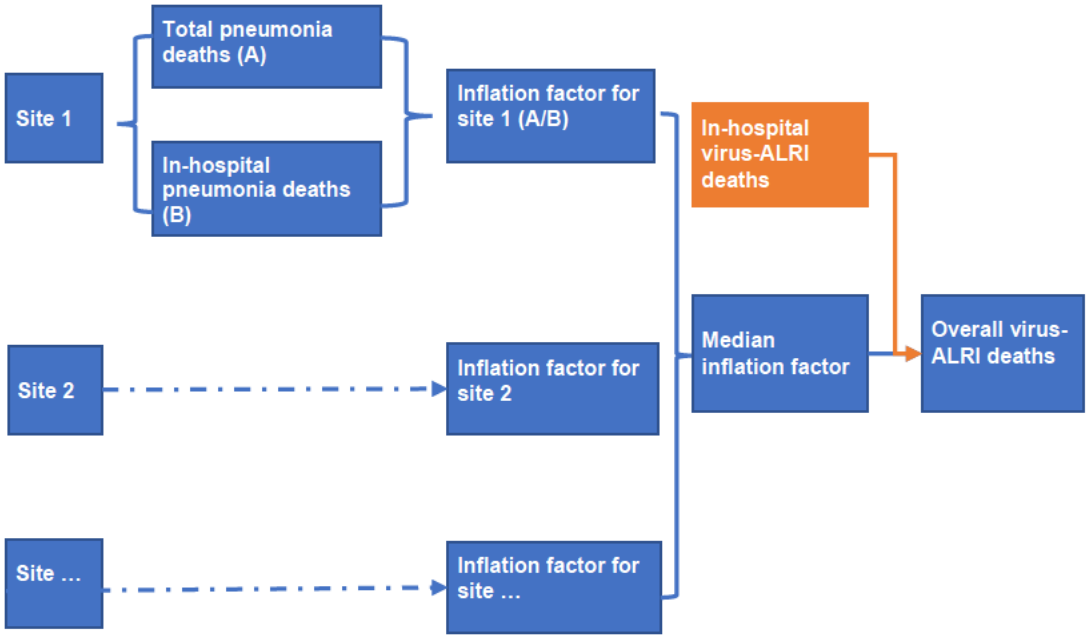

Figure 3-6. A schematic figure showing the estimation of the inflation factor and the overall virus–associated ALRI mortality.

The inflation factor of high child mortality countries might not be generalizable to countries with low child mortality due to the difference in care seeking and child nutrition condition between the two settings. Two types of data that were identified in published reports were considered good proxies for the inflation factor for countries with low child mortality. First, the US underlying cause of death database records deaths across the country (Centers for Disease Control and Prevention and National Center for Health Statistics). The data are available for the number of children under five years who died from pneumonia (ICD–10 J12–J18; underlying cause of death) at home, on arrival at medical facilities, in outpatient departments or emergency departments, in inpatient departments, and at other places from 1999 onward. The second type of data is the measure for childhood pneumonia care-seeking: the percent of children with pneumonia symptoms who received care at health providers as measured in Multiple Indicator Cluster Surveys, Demographic and Health Surveys, and other national surveys (UNICEF 2016). In this thesis, the second type of data was chosen because the data were available in more countries and places. The reciprocal of percent of children with pneumonia symptoms who received care at health

providers was estimated and used as a proxy for the inflation factor. The median inflation factor across regions and countries was applied to the in–hospital mortality estimate for low child mortality countries to yield the overall mortality of virus–associated ALRI deaths in that setting. In the case of IFV–associated mortality in the low child mortality setting, and the inflation factor was estimated using a different type of data – the US IFV–associated mortality data. The details are available in the chapter for IFV (Chapter 4).

(3) Sensitivity analysis

The overall virus–associated ALRI mortality was estimated using other approaches in sensitivity analysis. Approaches were tailored for each virus due to the different data availability by viruses. The details of the approaches are available in the chapter for each virus.

3.4.7. Virus–attributable ALRI mortality

The virus–attributable ALRI mortality was estimated by combining the virus–associated ALRI mortality and the corresponding attributable fraction (AF) for deaths. The AF for virus–associated ALRI mortality was modelled by assuming the hCFR for ALRI cases unattributed to a virus was the same with the hCFR for virus–negative cases (Figure 3–7).

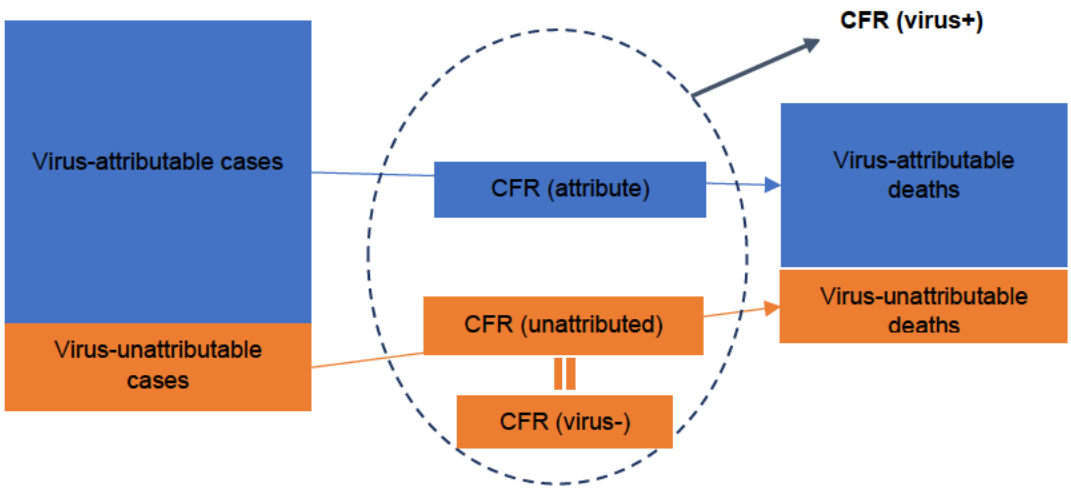

Figure 3–7. A schematic figure showing the estimation of attributable fraction for virus–associated ALRI deaths for children under five years.

The ratio between the case–fatality of the virus–positive and virus–negative cases could be estimated using data from hospital–based studies, in which at least 90% of cases were tested. The AF in virus–associated ALRI deaths was estimated by adjusting accordingly on the basis of the AF in cases using the following formulas.

Formula 3-3 $Deaths(virus+) = Cases(virus+) * CFR(virus+)$

Formula 3-4

$$Deaths(virus\_attri) = [Cases(virus+) * \frac{AFcase(\%)}{100}] * CFR(virus\_attri)$$

The Deaths (virus+) and Cases (virus+) denote the number of ALRI deaths and cases positive for a virus; the CFR (virus+) denotes case–fatality ratio for virus–positive ALRI cases. Similarly, the Deaths (virus_attri), Cases (virus_attri), and CFR (virus_attri) denote the deaths and cases attributed to the virus, and the CFRs for virus-attributed ALRI. The AFcase (%) denotes the AF (%) for virus–associated ALRI cases. Based on Formula 3–3 and 3–4, the AF (%) for virus–associated ALRI deaths could be estimated in Formula 3–5:

Formula 3-5 $AFdeaths(\%) = AFcase(\%) * \frac{CFR(virus\_attri)}{CFR(virus+)}$

The ratio of case–fatality of virus–attributable ALRI cases to virus–positive cases was estimated using the formulas below (Formula 3–6 and 3–7). The relationship between CFR (virus_attri), CFR (virus_non–attri), and CFR (virus+) is shown in Formula 3–7:

Formula 3-6

$$Deaths\ (virus+) = Deaths\ (virus\_attri) + Deaths(virus\_non-attri)$$

$$= [Cases(virus+) * \frac{AFcase(\%)}{100}] * CFR(virus\_attri) + [Cases(virus+) * \frac{100-AFcase(\%)}{100}] * CFR(virus\_non-attri)$$

Formula 3-7 (transformed from Formula 3–6)

$$CFR\ (virus+) = \frac{AFcase(\%)}{100} * CFR(virus\_attri) + \frac{100-AFcase(\%)}{100} * CFR(virus\_non-attri)$$

In Formula 3–7, the inputs for AFcase (%) were obtained from a previous published systematic review and two recent multi–country pooled analyses (Benet et al. 2017, Pneumonia Etiology Research for Child Health Study Group (PERCH) 2019, Shi et al. 2015). The CFR (virus_non–attri) denotes the CFR for the cases that were tested positive for the virus but not attributed to the virus. It was assumed that CFR (virus_non–attri) was equal to the CFR for virus–negative ALRI cases. The ratio of case–fatality of virus–positive cases versus virus–negative cases was estimated using data from hospital–based studies.

Sensitivity analysis

The virus-attributable mortality was also estimated using data from Child Health and Mortality Prevention Surveillance (CHAMPS) Network (CHAMPS) using another approach. CHAMPS tracks the causes of under-five mortality and stillbirths at seven sites in Sub-Saharan Africa and South Asia since December 2016. The seven sites are Baliakandi and Faridpur, Bangladesh; Bamako, Mali; Kersa and Harar, Ethiopia; Makeni, Sierra Leone; Manhiça, Mozambique; Siaya and Kisumu, Kenya; Soweto and Thembelihle, South Africa (Salzberg et al. 2019). For the current analysis, the percent of virus-attributable ALRI was estimated using (1) the number of all-cause ALRI deaths where ALRI could be anywhere in the causal pathway (underlying cause or condition, immediate cause or condition, co-morbid causes or conditions), and (2) the number of virus-ALRI deaths where virus could be anywhere in the causal pathway from December 2016 onward (CHAMPS). CHAMPS were conducted in high child mortality countries, so the estimated percent was applied to ALRI mortality for high child mortality settings.

Chapter 4 Global burden of seasonal influenza virus (IFV) –associated respiratory infections

4.1. Summary

Background

Seasonal influenza virus (IFV) is a common cause of ALRI in young children. A review in 2008 showed that IFV was associated with 20 million ALRI cases and one million severe ALRI in children under five years globally. Influenza vaccination for children and pregnant women can protect young children from influenza infections. However, only a few low– and middle– income countries have adopted routine influenza vaccine for children and pregnant women. Most of these countries have achieved only low vaccine uptake. Moreover, in the 2009 influenza pandemic, a newly emergent influenza strain (i.e., influenza A/H1N1pdm09) replaced the pre–existing seasonal influenza A subtype H1N1. The influenza burden might have changed due to the circulation of this new subtype.

Standardised analysis

The regional and global burden of influenza–associated respiratory infections in children under five years were estimated using data from a systematic review of studies and additional high–quality unpublished studies. A generalised linear mixed model was used to combine incidence rates, hospitalisation rates, and hCFRs of IFV–ALRI. The IFV–ALRI cases and hospitalisations were estimated by applying the pooled incidence and hospitalisation rates to 2018 population estimates. The IFV–ALRI in–hospital deaths were estimated by combining hospitalisations and pooled hCFRs of IFV–ALRI. Analysis was stratified by severity, region, and age. In the main analysis, global estimates were the sum of estimates by age and by child mortality settings. The IFV–ALRI overall mortality was estimated using the in–hospital deaths and a multiplier (“inflation factor”). As presented in Chapter 3, in the analysis of the inflation factor in high child mortality settings, input data were the number of all–cause pneumonia deaths among children

under five years in defined catchment areas by locations of death. Input data from low child mortality settings are presented below. Other adaptions to the standardised methods are also presented below.

The IFV–attributable burden were estimated using IFV–associated burden estimates and the attributable fraction (AF) for IFV–associated cases, which was obtained from one recent systematic review and two recent multi–country studies, and the AF for IFV–associated deaths, which was modelled using the AF for IFV cases and data from the present systematic review. A sensitivity analysis for the IFV–attributable burden was conducted using the proportion of IFV–attributable ALRI deaths derived using CHAMPS data.

Objective

To update estimates of the global number of cases, hospitalisations, and deaths from IFV–ALRI in children under five years for 2018.

4.2. Adaptation in the methods

4.2.1. Adaptation in data source – systematic review

(1) Timespan for systematic review of IFV

The current systematic review of the burden of seasonal IFV–associated respiratory infections was conducted to update a previous systematic review (Nair et al. 2011). Search strategies similar to the previous search were used to identify studies published between 1 January 2009 and 31 December 2018. Studies in the previous review were included. Chinese databases had not been searched in the previous review, so Chinese databases were searched to identify studies published between 1 January 1995 and 31 December 2018.

(2) Inclusion and exclusion criteria

- Studies were included if they reported community incidence rates of the entire spectrum of respiratory infections (from mild to severe

infections, including influenza–like illness, ALRI, and more severe infections) with laboratory–confirmed IFV in children under five years.

- Studies were excluded if they only reported the proportion of IFV among hospitalised ALRI cases because this measure has already been analysed in another systematic review (Lafond et al. 2016).
- Studies were excluded if they only reported estimates from the 2009 pandemic period (the year 2009 or 2009–2010 season). Studies were excluded if they reported combined data for the non–pandemic and pandemic periods, and data could not be stratified by non–pandemic and pandemic periods.

There were no adaptations in the case definitions, risk of bias assessment tool, morbidity estimation, in–hospital mortality estimation, and virus–attributable burden.

4.2.2. Overall mortality of IFV–ALRI

Main analysis

The inflation factor and overall mortality of IFV–ALRI in countries with high child mortality was estimated using the standardised approach in the main analysis. For countries with low child mortality, the inflation factor was estimated using the IFV–associated mortality data from the US Influenza–Associated Pediatric Mortality Surveillance System (US Centers for Disease Control and Prevention). The system reports data that are most relevant for estimating the inflation factor: location–specific deaths with laboratory–confirmed IFV infections in children aged under 18 years. For our analysis, we extracted the number of IFV–associated paediatric deaths occurring in communities, emergency departments, and hospitals over 14 years during 2004–2018 (excluding the pandemic year 2009–2010).

Sensitivity analysis

Another two approaches (Approach IFV 2 and Approach IFV 3) were used to estimate the inflation factor and the overall IFV–associated ALRI mortality for high child mortality countries in the sensitivity analysis.

Data required for the analysis included verbal autopsy confirmed pneumonia deaths in a defined catchment area and local concurrent influenza circulation data from severe acute respiratory infection (SARI) surveillance, both reported on a monthly basis. To be eligible, the number of pneumonia deaths were required to be at least 60 over three consecutive years. Five sites were identified with eligible data, including four sites in the INDEPTH Network, and another study conducted in Bangladesh shared by the Respiratory Virus Global Epidemiology Network. The estimation of the inflation factor is shown in Figure 4–1.

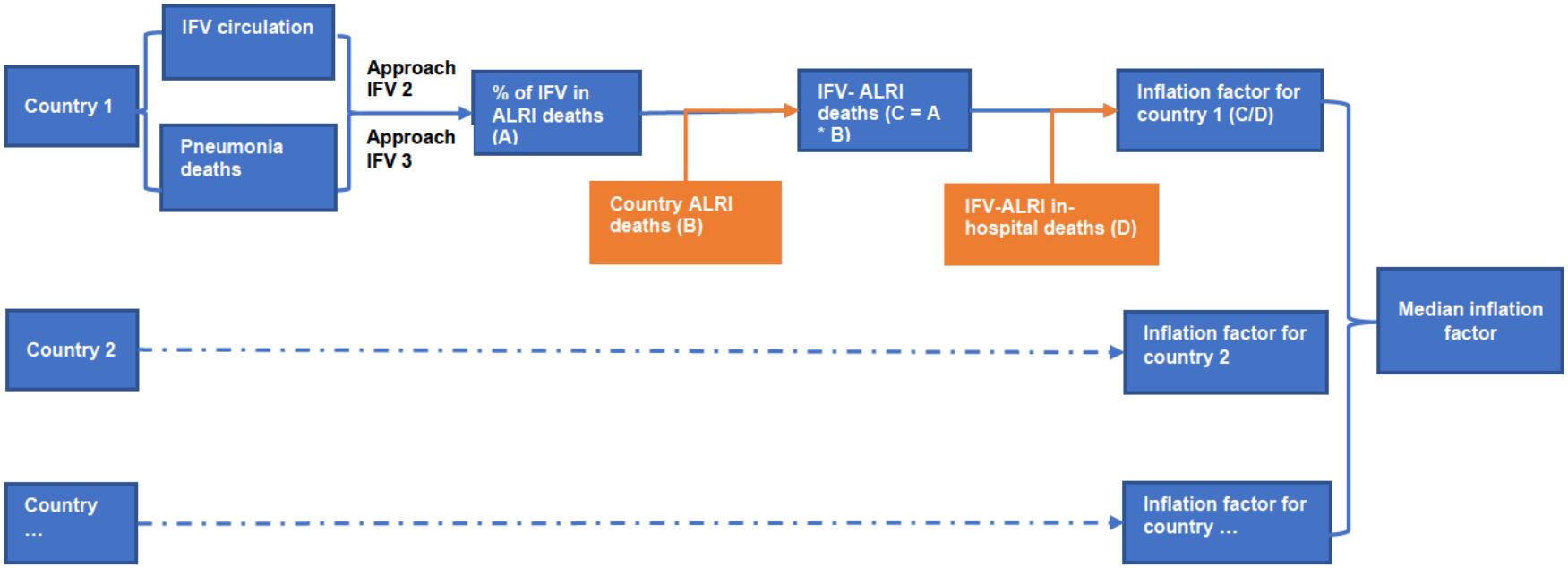

Figure 4-1. Approach IFV 2 and Approach IFV 3 –estimation of the inflation factor

- The country–specific IFV–ALRI overall deaths (**C** in Figure 4–1) were estimated by applying the proportion of IFV in ALRI deaths to country pneumonia deaths in children under five years.

- The country IFV–ALRI in–hospital deaths (**D** in Figure 4–1) were estimated using the country population estimate, and location–matched hospitalisation rate and hCFR for 0–59 months, where available (site–matched data in two sites; country–matched data in two sites). Otherwise, the meta–estimates for the corresponding region where the site belongs to were applied to the country population estimate (one site).

As shown in Figure 4–1, the major difference between Approach IFV 2 and Approach IFV 3 is how the proportion of IFV in ALRI deaths were estimated.

Approach IFV 2

Approach IFV 2 was similar to the model used in the previous IFV analysis wherein the excess pneumonia deaths during the influenza season compared with non–influenza–season months was associated with IFV (Nair et al. 2011). IFV (RSV) season was defined as any months with at least 10 samples tested and at least 10% of tested samples being positive. Whenever there was an overlap between IFV and RSV season, the excess pneumonia deaths within influenza season were proportionately attributed to the two pathogens. Assumptions are (1) the number of pneumonia deaths associated with other circulating pathogens and factors are the same within IFV seasons and outside seasons (no confounding effect); (2) the degree of association between the virus activity and the number of virus–associated pneumonia deaths was the same for IFV and RSV. There were no clear influenza seasons in two sites in Bangladesh and Kenya, so an inflation factor could not be estimated using this approach. The impact of IFV or any pathogens varies by year. It is possible to observe negative IFV-associated pneumonia deaths in certain years especially in a mild IFV season because of the difficulty in differentiating the excess deaths in IFV seasons from the total deaths (Li et al. 2017). Although the point estimate of IFV-associated deaths

is negative, the uncertainty intervals can be wide and overlap zero. Since the objective of this analysis was to estimate the average impact of IFV on pneumonia deaths, the negative excess deaths for one particular year were not set to zero.

Approach IFV 3

The Approach IFV 3 is a new method. The number of IFV–associated ALRI deaths is related to the influenza activity (i.e., the proportion of IFV in ALRI cases), the risk of mortality from IFV–ALRI compared with the risk of death from non–IFV–ALRI, and the number of ALRI deaths. Influenza activity and the number of ALRI deaths can vary by months throughout a year. Thus, the number of IFV–ALRI deaths were estimated on a monthly basis using Formula 4–1. The risk of mortality from IFV–ALRI was considered to be constant throughout a year.

Formula 4–1

$$\%\ IFV\ in\ ALRI\ deaths =$$

$$\sum_{1}^{\mathrm{k}}\left(\frac{\mathrm{PropIFVi} * \mathrm{RiskDeathIFV}}{(\mathrm{PropIFVi} * \mathrm{RiskDeathIFV} + (1 - \mathrm{PropIFVi}) * 1.00} * \mathrm{MonPNEi}\right) / \sum_{1}^{\mathrm{k}} \mathrm{MonPNEi}$$

In the formula, MonPNEi denotes the pneumonia deaths for the ith month, and PropIFVi denotes the IFV positivity for the ith month (%). The RiskDeathIFV denotes the risk of dying from IFV–ALRI compared with non–IFV–ALRI: the ratio of case–fatality of IFV–ALRI cases versus non–IFV–ALRI cases. The hCFR of IFV–ALRI and the hCFR for non–IFV–ALRI were estimated using data from hospital–based studies in which at least 90% of cases were tested. The risk of dying from IFV compared with non–IFV–ALRI (RiskDeathIFV) was estimated using the two hCFRs.

4.3. Results

During 1995–2018, 157 studies (123 new studies) were identified with data on community incidence of IFV–associated respiratory infections, hospitalisation rates, and hCFRs of IFV–ALRI. Of these studies, 57 were unpublished from the collaboration network and 100 were from published literature. By World Bank income regions, 14 studies (9%) were from LICs, 48 (31%) from LMICs, 29 (18%) from UMICs, 62 (39%) from HICs, and four studies from multiple countries from mixed World Bank income regions. Figure 4–2 shows the study selection for the systematic review on seasonal influenza. A summary of included studies for each outcome are in appendix (A18). Details of included studies are in Appendix A19.

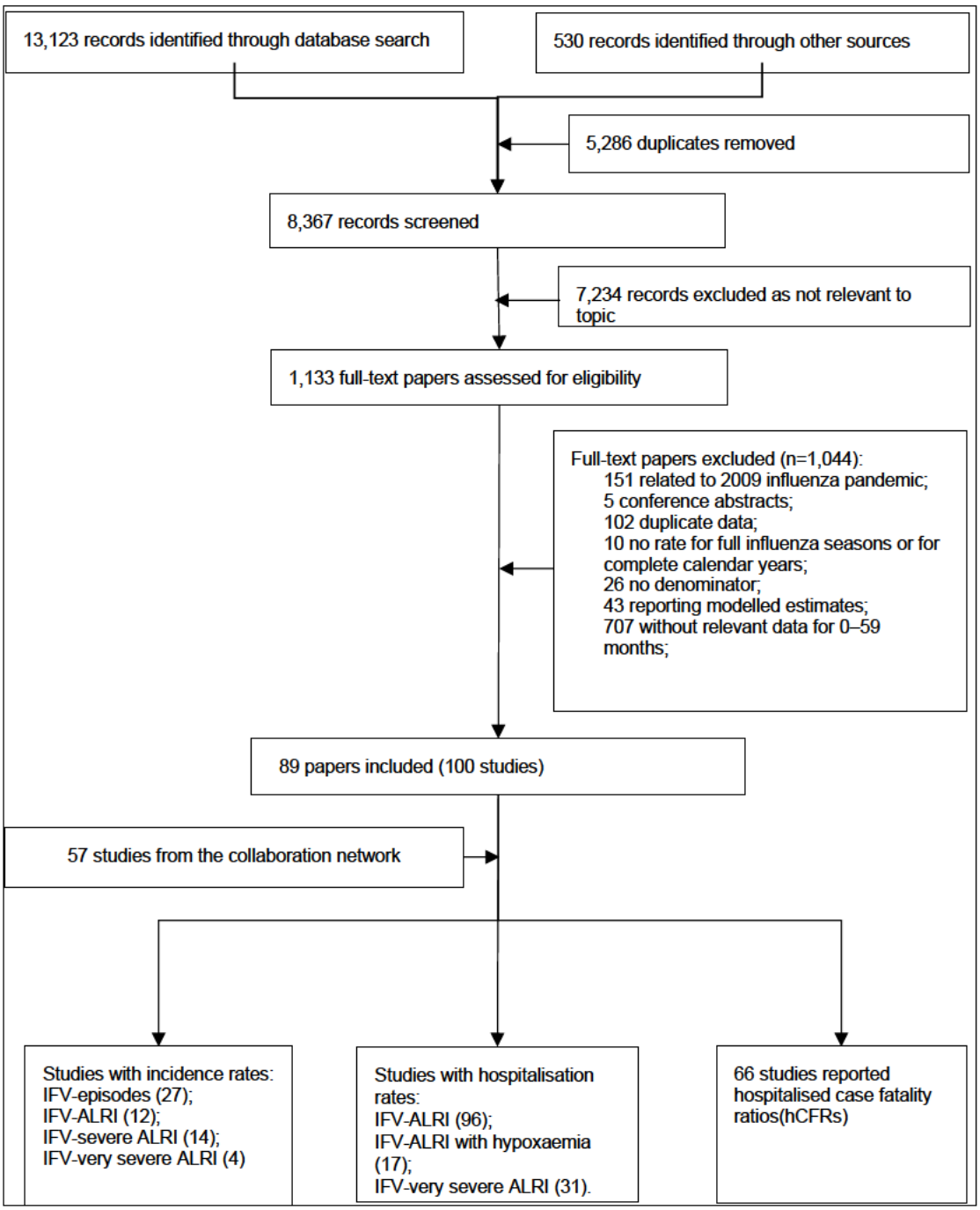

Figure 4-2. Flow diagram for selection of studies for seasonal influenza.

For multi–site papers, the site–specific data were extracted where available and were analysed as one study; in this way 100 studies were extracted from 89 papers. One study could provide data on multiple outcomes in the same population, thus the total number of studies was greater than the sum of studies by outcomes.

4.3.1. The burden of IFV–associated respiratory infections in the community

There were 38 community–based studies with data on incidence rates. These studies included 27 studies with data on IFV–episodes (the entire spectrum of respiratory infections associated with IFV), 12 studies for IFV–ALRI, 14 studies for IFV–severe ALRI, and 4 studies for IFV–very severe ALRI (Appendix A19).

Incidence rates of IFV–episodes and the number of cases

After imputation, 18 studies with incidence rates for 0–59 months were included in the meta–analysis. These studies were from South Africa, Australia, the US (two studies), Japan (two studies), Finland, Senegal (two studies), Switzerland, India (two studies), Vietnam, Bangladesh (two studies), Romania, Spain, and Nicaragua. Eight studies were from high child mortality settings; eight studies were from LMICs, one study from UMICs, and nine studies from HICs. Eight studies reported the rates for pre–2010 period. One study was identified with an influential incidence rate of IFV–episodes for 0–59 months. A given study is considered influential if the exclusion of this study leads to considerable changes in the meta–estimates as mentioned in Chapter 3. This study reported a very low incidence rate (1.4 per 1,000 children per year) of IFV–associated ILI cases presenting to public healthcare facilities across Romania. No other studies were identified with data for this outcome in Romania.

The incidence rate meta–estimate for IFV-episodes was 175.2 (95%CI 101.5–302.3) per 1,000 children per year for 0–59 months for high child mortality settings, and 42.4 (95%CI 17.1–105.0) for low child mortality settings. These meta–estimates translated to 88.3 million (UR 49.6–159.2) IFV–episodes globally in children under five years (Table 4–1).

In sensitivity analysis, the global number of IFV–episodes for children under five years was 109.5 million (UR 63.1–190.6) in the stratified analysis by country development status (Appendix A8). There was only one study in UMICs, so it is

impossible to estimate the global number of IFV–episodes in the stratification by World Bank income regions.

Incidence rates of IFV–ALRI and the number of cases

After imputation, there were 12 studies with data on incidence rates of IFV–ALRI among children aged 0–59 months. Studies were from Australia, Finland, Germany, the US, India (three studies), Bangladesh (two studies), Nicaragua, Pakistan, and South Africa. No potentially influential studies (significantly affecting the combined estimates) were identified for this outcome.

The incidence rate meta–estimate of IFV–ALRI was 15.6 (95%CI 10.3–23.6) for 0–59 months in high child mortality settings, and 9.3 (95%CI 7.5–11.5) in low child mortality settings. In 2018, 9.1 million (UR 6.4 –13.2) IFV–ALRI cases were estimated to occur among children aged 0–59 months globally. In sensitivity analysis, the global number of IFV–ALRI cases was 10.1 million (UR 6.8–15.1) in the stratification by country development status (Appendix A8).

Incidence rates of IFV–severe ALRI and IFV–very severe ALRI and the number of cases

After imputation, there were seven studies with data on incidence rates of IFV–severe ALRI for 0–59 months, and four studies for IFV–very severe ALRI. All studies were from high child mortality countries. It was estimated that there were 1.1 million (UR 0.5–2.5) IFV–severe ALRI cases, and 0.3 million (UR 0.1–1.2) IFV–very severe ALRI cases among children under five years in high child mortality countries (Appendix A8).

Table 4-1. Estimates of the incidence (per 1,000 children per year) and number of IFV–episodes and IFV–ALRI cases in children under five years in 2018, by World Bank income regions and child mortality settings*

		LMICs	UMICs	HICs	High child mortality	Low child mortality	Global†
IFV–episodes							
0–5 m	Studies	9	1	0	10	..	
	Incidence‡	80.2 (40.9–151.6)	..	..	80.8 (44.2–143.1)	..	
	Episodes (*1,000)	3,552 (1,848–6,831)	..	..	3,720 (2,070–6,688)	..	..
6–11 m	Studies	2	1	0	2	..	
	Incidence	165.9 (93.2–277.8)	..	..	164.8 (92.6–276.2)	..	
	Episodes (*1,000)	7,233 (4,201–12,457)	..	..	7,519 (4,367–12,950)	..	..
12–59 m	Studies	2	1	3	2	3	
	Incidence	138.6 (57.2–299.4)	..	147.3 (82.6–248.9)	138.6 (57.2–299.4)	147.3 (82.6–248.9)	
	Episodes (*1,000)	47,524 (20,871–108,280)	..	7,467 (4,315–12,926)	49,420 (21,703–112,599)	27,019 (15,614–46,773)	76,439 (37,317–159,372)
0–59 m	Studies	8 (3)§	1	9 (3)	8 (3)	10 (3)	
	Incidence	175.2 (101.5–302.3)	..	61.9 (32.5–117.9)	175.2 (101.5–302.3)	42.4 (17.2–104.8)	
	Episodes (*1,000)	75,538 (43,911–129,996)	..	3,925 (2,068–7,453)	78,545 (45,659–135,170)	9,735 (3,955–23,974)	88,280 (49,615–159,145)
IFV–ALRI cases							
0–5 m	Studies	4	1	0	5	..	
	Incidence	4.9 (2.2–10.8)	..	..	8.5 (2.6–26.9)	..	
	Episodes (*1,000)	217 (98–479)	..	..	391 (122–1,251)	..	..

* Meta-analyses were only done when there were two or more studies. ..=not available.
† Global burden estimates were developed by summing up estimates for 0–59 months by child mortality settings.
‡ Incidence (per 1,000 children per year) were estimated using generalised linear mixed models.
§ Data in parentheses was the number of imputed studies. Data were imputed using a multiple imputation approach.

Global burden of acute lower respiratory infection (ALRI) associated with influenza virus, human metapneumovirus, and human parainfluenza virus among children under five years

		LMICs	UMICs	HICs	High child mortality	Low child mortality	Global†
6–11 m	Studies	4	1	0	5	..	
	Incidence	28 (23.6–33.3)	..	..	27.6 (23.4–32.6)	..	
	Episodes (*1,000)	1,229 (1,036–1,459)	..	..	1,259 (1,068–1,485)	..	..
12–59 m	Studies	4	1	0	5	..	
	Incidence	16.7 (8.6–32.3)	..	..	15.6 (8.9–27.1)	..	
	Episodes (*1,000)	5,727 (2,966–11,062)	..	..	5,563 (3,198–9,681)	..	..
0–59 m	Studies	7 (3)	1	4 (3)	8 (3)	4 (3)	
	Incidence	14.6 (9.2–23.3)	..	9.3 (7.5–11.5)	15.6 (10.3–23.6)	9.3 (7.5–11.5)	
	Episodes (*1,000)	6,299 (3,961–10,021)	..	590 (477–729)	7,001 (4,647–10,550)	2,135 (1,728–2,638)	9,136 (6,375–13,188)

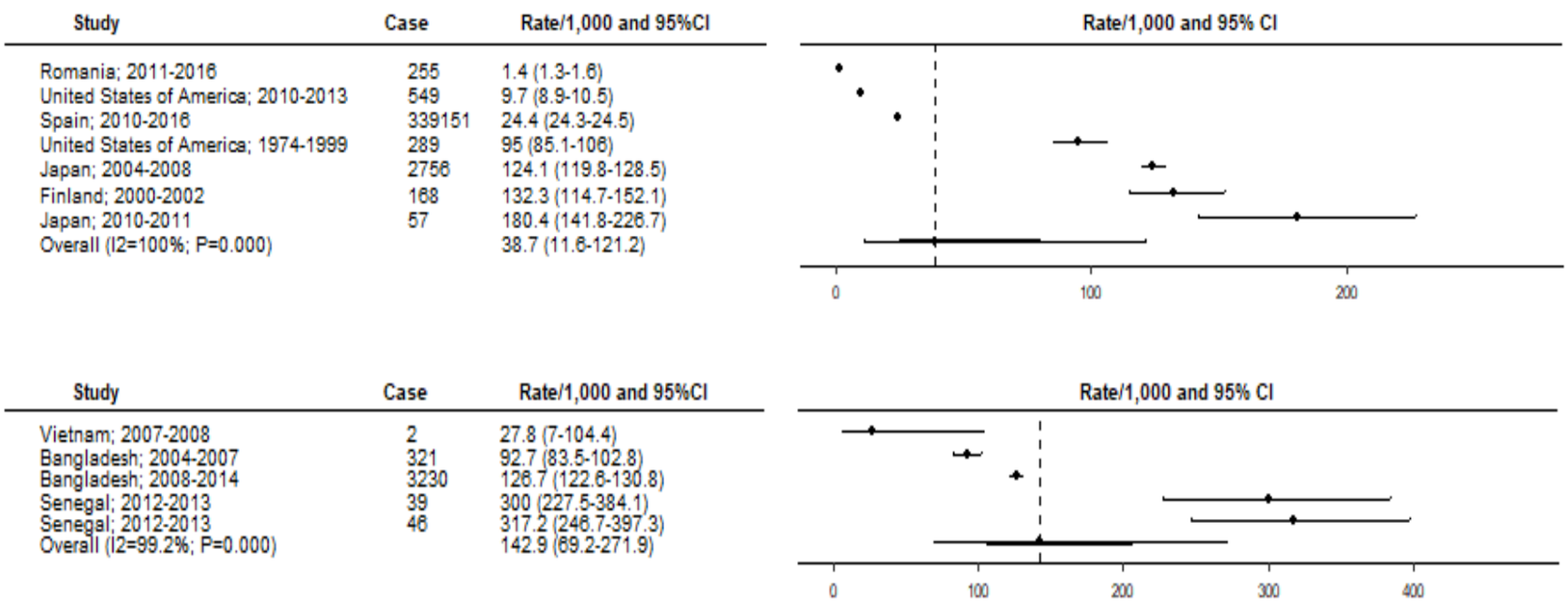

Figure 4-3. Forest plot of non-imputed incidence rates of IFV–episodes for children aged 0–59 months by child mortality settings.

Upper: low child mortality settings; below: high child mortality settings. The forest plots did not include imputed data because using the multiple imputation method, a group of values were imputed for each study. The pooled incidence rate point estimate in high child mortality settings increased after imputation. This was mainly driven by one study in Nicaragua reporting a high rate for 0–23 m (218 per 1,000 children per year). This study was not included in the forest plot because it did not report data for 0–59 m. After imputation, rates for 0–59 m in this study were included in the meta–analysis.

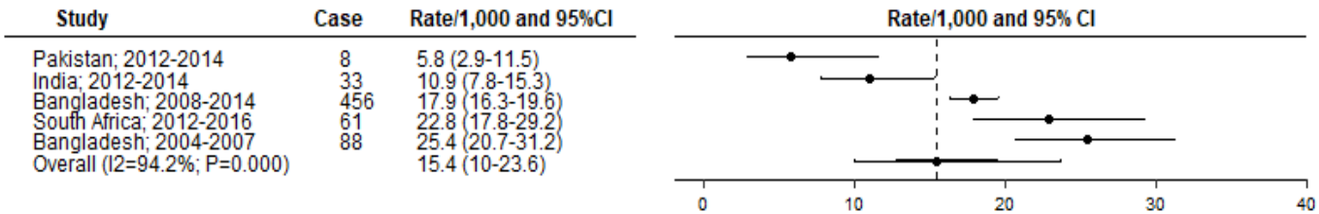

Figure 4-4. Forest plot of non-imputed incidence rates of IFV–ALRI for children aged 0–59 months for high child mortality settings.

The forest plot did not include imputed data because using the multiple imputation method, a group of values were imputed for each study. Data for low child mortality settings were not plotted because there was only one study with data for 0–59 months (non-imputed data).

4.3.2. IFV–associated ALRI burden in the hospital setting

Hospitalisation rates and hospitalisations of IFV–associated ALRI

There were 96 studies with data on IFV–ALRI hospitalisation rates, including 59 studies with data by three narrow age bands (i.e., 0–5 months, 6–11 months, or 12–59 months) (Appendix A19). As shown in Figure 4–5, Figure 4–6, and Figure 4–7, the hospitalisation rates ranged from 0 to 25.1 (95%CI 21.3–29.5) per 1,000 children per years for 0–5 months, 0.6 (95%CI 0.2–1.6) to 37.0 (95%CI 32.7–41.8) per 1,000 children per year for 6–11 months, and 0.1 (95%CI 0–0.5) to 27.7 (95%CI 23.4–32.7) per 1,000 children per year for 12–59 months across studies. By narrow age groups three studies were identified with potentially outlying hospitalisation rates; no influential studies were identified. Two of the three studies reported the highest hospitalisation rates by age groups, one Chinese study (2010–2012) and one Japanese (2002–2008). Both studies included children hospitalised with ARI and fever, and accounted for healthcare utilization when estimating rates. The Japanese study used individually recorded person-time as the denominator to estimate rates. The third study reported a very low hospitalisation rate for 0–5 months (0.2 per 1,000 children per year) in Kamalapur, Bangladesh during 2007–2015. The hospitalisation rate of IFV–ALRI in children aged 0–59 months in this study were broadly similar with another Bangladeshi study (0.7 vs 0.4 per 1,000 children per year).

The meta-estimate of IFV–ALRI hospitalisation rate was 2–5–fold higher in infants (1.5–4.7 per 1,000 children per year) than children aged 12–59 months (0.8–1.2 per 1,000 children per year) across World Bank income regions and child mortality settings (Table 4–2). There were 854,000 (UR 514,000–1,450,000) IFV–ALRI hospitalisations among children under five years globally according to the analysis by child mortality settings. About 24% and 21% of the hospitalisations were in infants aged 0–5 months and 6–11 months,

respectively. An estimated 420,000 (UR 261,000–677,000) IFV–ALRI hospitalisations occurred in LMICs.

The estimates of global hospitalisations of IFV–ALRI for children under five years ranged from 786,000 to 870,000 across different stratification groups, with wide and overlapping uncertainty ranges (Appendix A8).

Hospitalisation rates and hospitalisations of IFV–associated ALRI with hypoxaemia and IFV–associated very severe ALRI

An estimated 223,000 (UR 116,000–501,000) hospitalisations of IFV–ALRI with hypoxaemia occurred among children under five years globally, accounting for 26% of IFV–ALRI hospitalisations (Table 4–2). For IFV–very severe ALRI, 87,000 (UR 23,000–538,000) hospitalisations were estimated to occur in children under five years globally, accounting for 10% of IFV–ALRI hospitalisations (Table 4–2).

hCFRs of IFV–associated ALRI and in–hospital mortality

A total of 66 studies reported hCFRs for IFV–ALRI in children under five years, including 28 studies with data on three age bands. hCFRs of studies that were included in the main analysis are in Table 4–5. Additional details are in Appendix A19. The hCFR meta-estimates were highest in high child mortality settings and LMICs, ranging from 2.3 to 3.2% by age groups in high child mortality settings and from 3.2 to 8.1% by age groups in LMICs (Table 4–3). The hCFR meta-estimates of IFV–ALRI were lower in low child mortality settings (0.4–0.8% by age groups). In the stratified analysis by child mortality settings, 13,000 (UR 4,900–52,500) IFV–ALRI in–hospital deaths were estimated to occur in children under five years globally, with 27% and 22% among infants aged 0–5 months and 6–11 months, respectively. About 82% of IFV–ALRI in–hospital deaths occurred in LMICs (calculated in the analysis stratified by World Bank income regions).

In the stratified analysis by country developing status, 15,300 (UR 5,800–43,800) IFV–ALRI in–hospital deaths were estimated to occur globally in children under five years. The estimate was 20,800 (UR 7,800–65,700) in the stratified analysis by World Bank income regions (Appendix A8).

Table 4-2. Estimates of hospitalisation rates (per 1,000 children per year) and hospitalisations of IFV–ALRI in children under five years in 2018, by World Bank income regions and child mortality settings *

		LMICs	UMICs	HICs	Low child mortality	High child mortality	Global†
IFV-ALRI							
0–5 months	Studies	13	9	13	16	19	
	Rate‡	1.8 (1.1–3.1)	3.7 (1.8–7.4)	4.4 (3.1–6.3)	4.7 (3.2-6.8)	2.1 (1.3-3.2)	
	Hospitalisations (*1,000) (A)	80 (48-133)	68 (34-138)	28 (20-40)	108 (74-158)	97 (62-151)	205 (136-309)
6–11 months	Studies	11	8	9	12	16	
	Rate	1.5 (1–2.4)	3.8 (1.7–8.3)	3.5 (1.4–8.8)	4.4 (1.9-9.8)	1.7 (1.2-2.3)	
	Hospitalisations (*1,000) (B)	66 (43-102)	70 (32-154)	22 (9-55)	101 (45-229)	78 (56-107)	179 (101-336)
12–59 months	Studies	17	11	20	26	22	
	Rate	0.8 (0.5–1.3)	0.8 (0.3–2)	1.2 (0.6–2.2)	1.2 (0.6-2.1)	0.7 (0.4-1)	
	Hospitalisations (*1,000) (C)	274 (171-441)	117 (46-301)	61 (32-116)	220 (118-410)	250 (158-394)	470 (276-804)
0–59 months	Hospitalisations (*1,000) (A+B+C)	420 (261-677)	255 (111-593)	111 (60-211)	430 (237-797)	424 (276-652)	854 (514-1450)
IFV- ALRI with hypoxaemia							
0–5 months	Studies	8	2	..	..	8	
	Rate	0.9 (0.5–1.6)	0.9 (0.5–1.5)	..	..	1 (0.6-1.6)	
	Hospitalisations (*1,000) (D)	40 (22-71)	17 (10-29)	..	..	46 (28-75)	..
6–11 months	Studies	8	2	..	..	8	
	Rate	0.7 (0.3–1.4)	1 (0.7–1.6)	..	..	0.8 (0.6-1)	
	Hospitalisations (*1,000) (E)	31 (14-66)	18 (12-28)	..	..	37 (28-47)	..
12–59 months	Studies	8	..	2	2	9	
	Rate	0.2 (0.1–0.4)	..	0 (0–1.3)	0 (0–1.3)	0.2 (0.1-0.3)	

* ..: not available.
† Global burden estimates were developed by summing up estimates in three non–overlapping age groups (0–5 m, 6–11 m, and 12–59 m), and in developing and industrialised countries classified according to UNICEF definition.
‡ Hospitalisation rates (per 1,000 children per year) were estimated using generalised linear mixed models.

Global burden of acute lower respiratory infection (ALRI) associated with influenza virus, human metapneumovirus, and human parainfluenza virus among children under five years

		LMICs	UMICs	HICs	Low child mortality	High child mortality	Global[†]
	Hospitalisations (*1,000) (F)	69 (34-137)	--	0 (0–15)	0 (0–15)	71 (41-123)	72 (41-138)
0–59 months	Hospitalisations (*1,000) (D+E+F)	139 (71-274)	--	--	69 (19-256)[§]	154 (98-245)	223 (116-501)
IFV-very severe ALRI							
0–5 months	Studies	9	3	2	4	9	
	Rate	0.6 (0.2–1.4)	0.2 (0.1–0.4)	0.3 (0.1–0.7)	0.3 (0.1-0.5)	0.3 (0-1.4)	
	Hospitalisations (*1,000) (G)	27 (10-70)	4 (2–7)	2 (1–5)	7 (3-15)	14 (1-228)	21 (4-243)
6–11 months	Studies	9	3	2	4	9	
	Rate	0.5 (0.3–0.9)	0.3 (0.1–1)	0.1 (0–0.6)	0.3 (0.1-0.8)	0.5 (0.2-0.9)	
	Hospitalisations (*1,000) (H)	22 (13-38)	6 (2-17)	1 (0-7)	7 (2-19)	23 (11-48)	30 (13-68)
12–59 months	Studies	9	5	8	11	11	
	Rate	0.1 (0–0.3)	0.1 (0–0.2)	0 (0–0)[**]	0 (0-0.1)	0.1 (0-0.2)	
	Hospitalisations (*1,000) (I)	34 (4-263)	15 (2-92)	0 (0-0)	1 (0-4)	36 (6-223)	37 (6-227)
0–59 months	Hospitalisations (*1,000) (G+H+I)	83 (27-371)	24 (6-116)	3 (1-12)	15 (6-39)	72 (17-499)	87 (23-538)

[§] For low child mortality settings, four studies reported the hospitalisation rates of IFV–ALRI with hypoxaemia for 0–59 m; the meta–estimate was 0·3 (0.1–1·4), translating to 69,000 (UR 19,000–256,000) hospitalisations.
[**] The rate was 1.4e-5 (9.7 e-6 to 2.0e-5), thus was rounded to 0 (0–0).

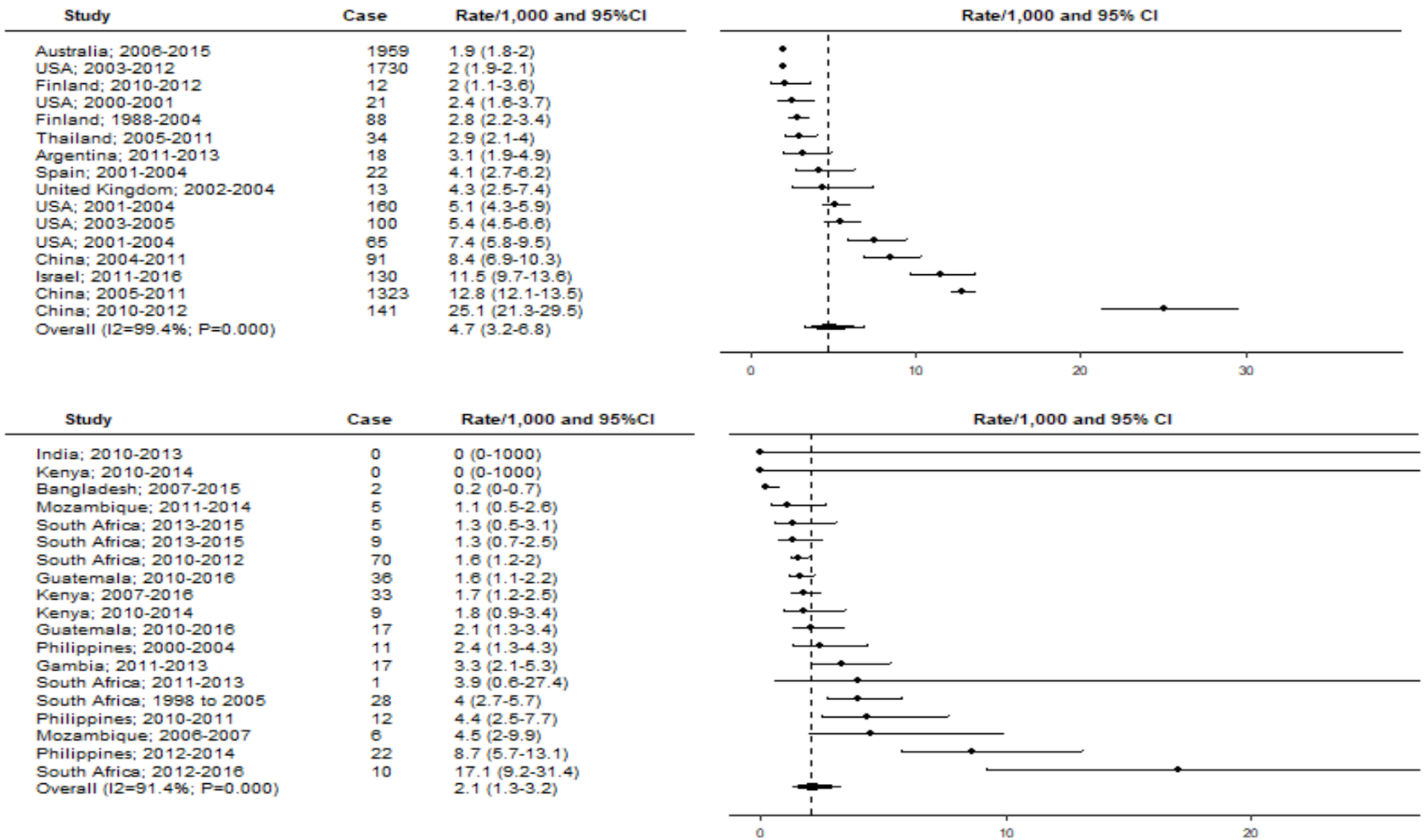

Figure 4-5. Forest plot of hospitalisation rates of IFV–ALRI for children aged 0–5 months by child mortality settings.

Upper: low child mortality settings. Below: high child mortality settings.

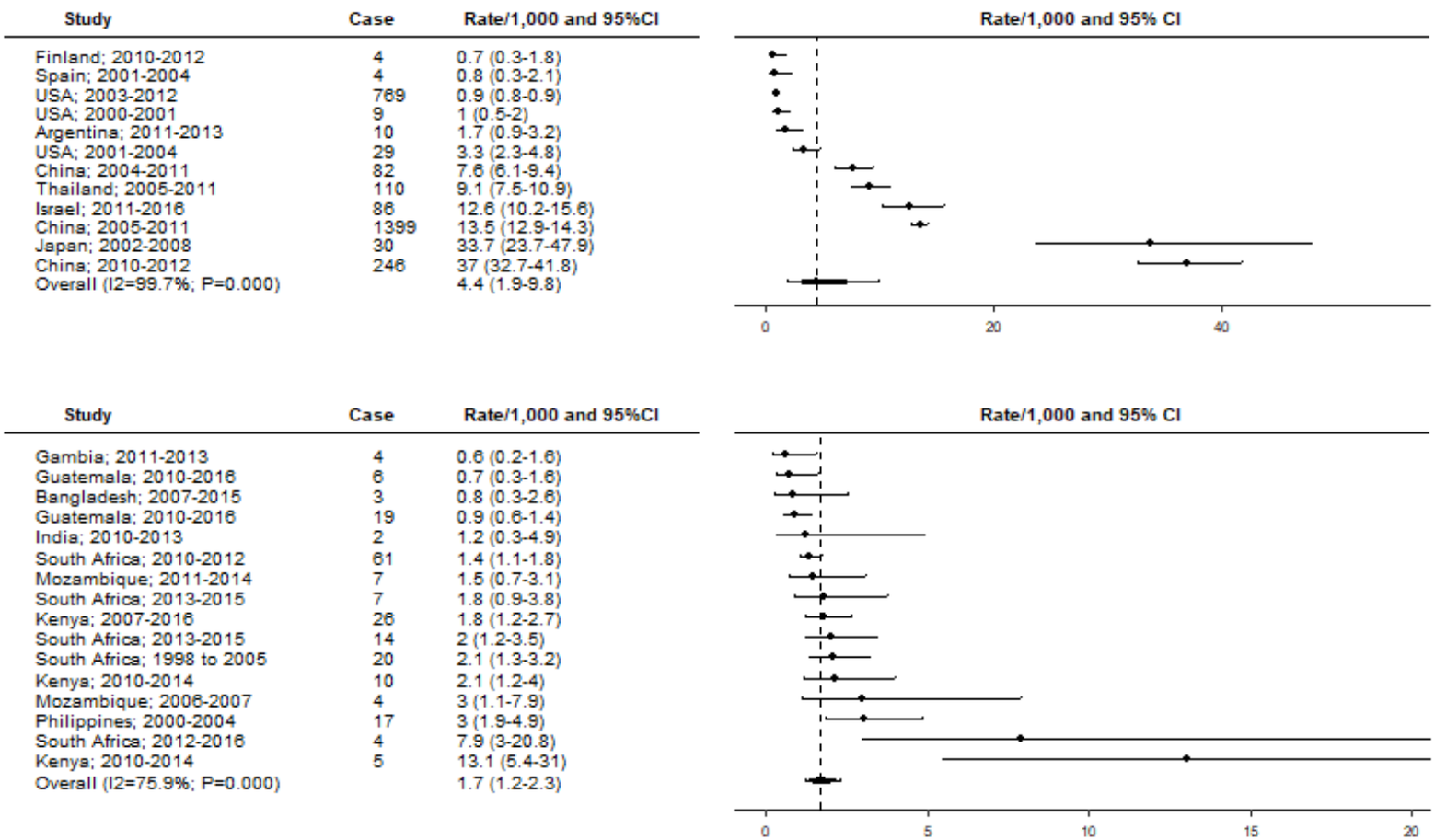

Figure 4-6. Forest plot of hospitalisation rates of IFV–ALRI for children aged 6–11 months by low child mortality settings.

Upper: low child mortality settings. Below: high child mortality settings.

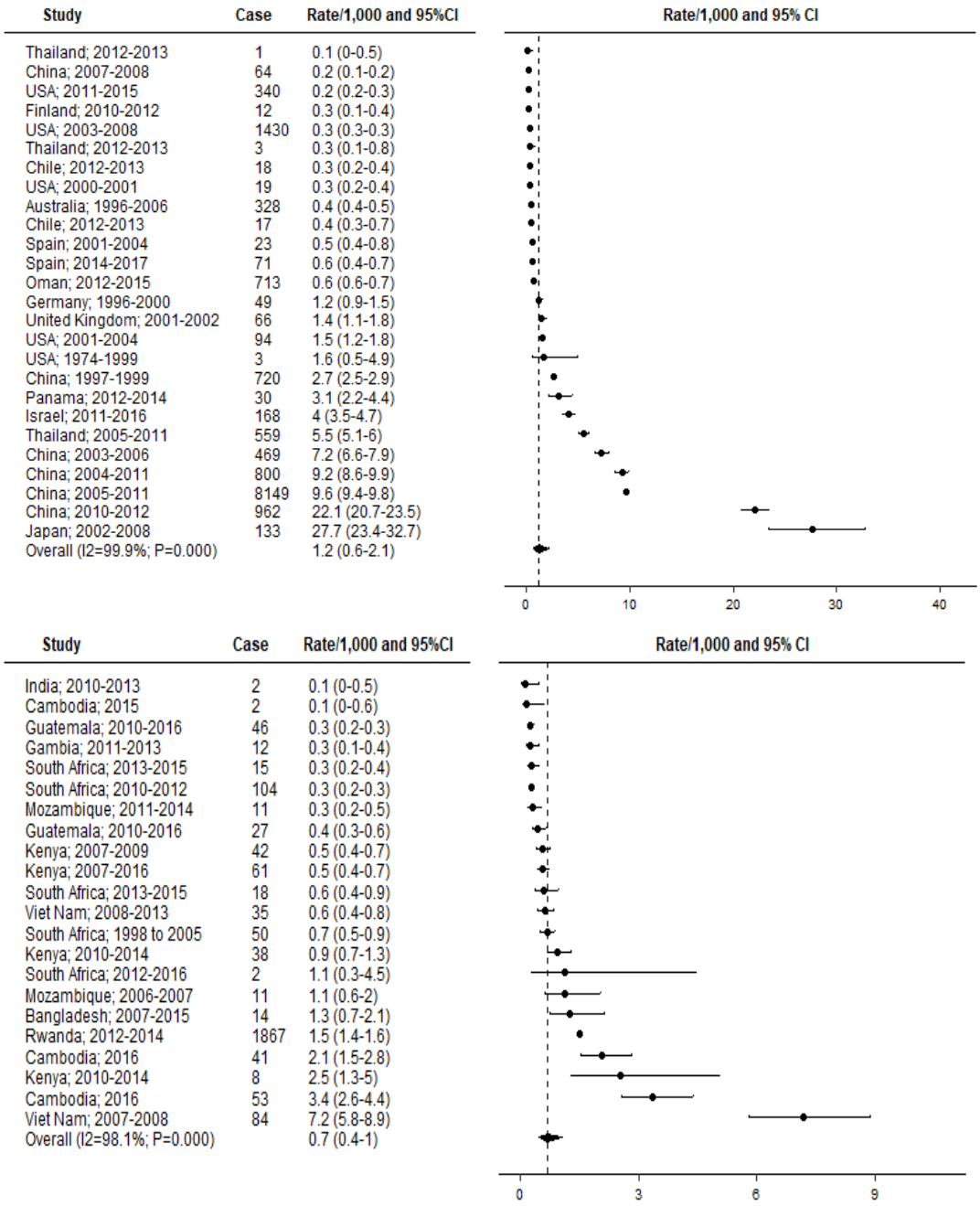

Figure 4-7. Forest plot of hospitalisation rates of IFV–ALRI for children aged 6–11 months by low child mortality settings.

Upper: low child mortality settings. Below: high child mortality settings.

Table 4-3. In–hospital case fatality ratio (hCFR) meta–estimates and in–hospital deaths in children with IFV–ALRI in children under five years in 2018, by World Bank income regions and child mortality settings

		LMICs	UMICs	HICs	Low child mortality	High child mortality	Global *
	Studies †	10	11	7	11	17	
0–5 months	hCFR (%)‡	3.2 (0.6–15.4)	2.6 (0.9–7.5)	0.5 (0–4.6)	0.8 (0.1–5.6)	2.7 (1–7.2)	
	Deaths (A)	2,500 (500–13,800)	1,800 (500–6,200)	100 (0–4,100)	900 (100–6500)	2600 (900–7600)	3500 (1000–14000)
6–11 months	hCFR (%)	8.1 (4.1–15.3)	0.7 (0.1–7.4)	0.8 (0.2–3.2)	0.4 (0–7.6)	3.2 (1.1–8.5)	
	Deaths (B)	5,300 (2,400–11,600)	500 (0–4,700)	200 (0–900)	400 (0–16300)	2500 (800–7200)	2900 (900–23400)
12–59 months	hCFR (%)	3.3 (1.7–6.3)	0.8 (0.3–2.2)	0.4 (0.1–2.1)	0.4 (0.1–1.5)	2.3 (1.3–3.9)	
	Deaths (C)	9,100 (4,000–20,100)	900 (200–3,700)	200 (0–1,300)	900 (200–3800)	5800 (2800–11600)	6600 (3000–15300)
0–59 months	Deaths (A+B+C)	17,000 (6,900–45,100)	3,200 (800–14,400)	600 (100–6,200)	2200 (300–26500)	10900 (4600–26200)	13000 (4900–52500)

* Global estimates were calculated by summing up estimates in three non-overlapping age groups (0–5 m, 6–11 m, and 12-59 m), and in developing and industrialised countries according to UNICEF definition.
† hCFR meta-estimates were based on studies providing data for the three non-overlapping age bands.
‡ hCFRs were estimated using generalised linear mixed models.

Table 4-4. Estimates of in–hospital case fatality ratios (hCFRs) in individual studies included in the main analysis.

Location (study period)	0 – 5 months		6 – 11 months		12 – 59 months	
	Deaths (No.)	hCFRs (%)	Deaths (No.)	hCFRs (%)	Deaths (No.)	hCFRs (%)
Australia (2011-2013)	0	0	0	0	0	0
Siaya County, Kenya (2010-2014)	0	0	0	0	1	2.6
Tone and Cinkasse districts, Togo (2011-2013; 2014-2015)	0	0	0	0	0	0
Soweto, Gauteng, South Africa (1998 to 2005)	1	3.6	2	10	1	2
Manhiça, Mozambique (2011-2014)	0	0	1	14.3	0	0
Kilifi, Kenya (2007-2016)	2	6.1	3	11.5	2	3.4
Nha Trang city, Vietnam (2008-2013)	0	0	0	0	0	0
Berlin, Germany (2010-2014)	0	0	0	0	0	0
Basse, The Gambia (2011-2013)	0	0	0	0	0	0
Nakhon Phanom and Sa Kaeo Provinces, Thailand (2005-2011)	0	0	0	0	1	0.2
David City, Panama (2012-2014)	3	21.4	2	13.3	0	0
Buenos Aires, Argentina (2008-2010)	0	0	0	0	0	0
Turku, Finland (2010-2012)	0	0	0	0	1	8.3
Aurora, Colorado, United States (2011-2015)	0	0	2	1.9	3	0.8
Paarl, South Africa (2012-2016)	1	10	0	0	0	0
Quetzaltenango, Guatemala (2010-2016)	0	0	1	5.3	1	2.2
Santa Rosa, Guatemala (2010-2016)	2	11.8	2	33.3	2	7.4
Valencia Region, Spain (2014-2017)	1	2.6	0	0	0	0
Buenos Aires, Argentina (2009-2016)	1	4.8	0	0	2	4.1
Soweto, South Africa (2015-2017)	0	0	0	0	0	0
Rabat, Morocco (2010-2011)	0	0	0	0	1	6.2
Lusaka, Zambia (2011-2013)	3	27.3	1	14.3	2	15.4

Location (study period)	0 – 5 months		6 – 11 months		12 – 59 months	
	Deaths (No.)	hCFRs (%)	Deaths (No.)	hCFRs (%)	Deaths (No.)	hCFRs (%)
Soweto, South Africa (2011-2013)	0	0	1	6.7	1	4.8
Klerksdorp, South Africa (2013-2015)	0	0	0	0	0	0
Pietermaritzburg, South Africa (2013-2015)	1	11.1	0	0	0	0
Soweto, Gauteng, South Africa (2009-2012)	1	1.4	0	0	1	1
Concepcion, Chile (2012-2013)	1	8.3	0	0	0	0
Iquique, Chile (2012-2013)	0	0	0	0	0	0

4.3.3. Overall mortality of IFV–associated ALRI

Of the eight sites with data on pneumonia deaths in hospitals and communities in high child mortality settings, five sites were from rural areas, and six from African countries. The inflation factor ranged from 1.5 to 3.5 across the eight sites, with a median value of 2.2. For low child mortality settings, an inflation factor of 1·6 (range 1.3–1.9 across 14 years) was estimated using the US paediatric IFV–associated deaths data. Using the two inflation factors, the overall IFV–ALRI mortality was estimated to be 27,400 (UR 10,600–100,000) in children under five years globally, including 23,900 (UR 10,100–57,600) in high child mortality settings, and 3,500 (UR 500–42,500) in low child mortality settings (Table 4–4). Using Approach 2 and Approach 3, the inflation factor was estimated to be 3.0 and 4.1, respectively (Appendix A12). Using the two approaches, the overall mortality point estimate could increase by 36–75%, with wide and overlapping uncertainty ranges (Appendix A12).

4.3.4. IFV–attributable burden estimates

Based on a median AF of 80% for IFV–ALRI, about 7.3 million (UR 5.1–10.6) ALRI cases and 683,000 (UR 411,000–1,160,000) ALRI hospitalisations could be attributed to IFV in children under five years (Table 4–6).

The ratio of case–fatality of IFV–attributable cases to IFV–associated cases was 0.9 according to eight hospital–based studies. Therefore, the AF for IFV–associated ALRI deaths was estimated to be 72% (Table 4–5). This suggested that 19,700 (UR 7,700–72,000) overall ALRI deaths could be attributed to IFV globally, including 17,200 (UR 7,300–41,500) deaths in high child mortality countries (Table 4–7).

Using CHAMPS data, the proportion of IFV–attributable ALRI deaths was 3.0% (95%CI 1.1–6.4) in children aged 1–59 months and 1.0% (95%CI 0.2–5.8) for neonates (deaths enrolled from December 2016 to December 2019). According

to the proportion, 20,100 (UR 8,100–53,700) ALRI deaths could be attributed to IFV among children under five years for high child mortality settings (Appendix A16).

Table 4-5. Inflation factor and the overall IFV–ALRI mortality estimates among children under five years.

Setting	Site	Ratio of all pneumonia deaths over in–hospital deaths for 0–59 months (A)	Inflation factor (B=median of A)	In–hospital mortality of IFV–ALRI (C)	Overall IFV–ALRI mortality (D=B*C)
High child mortality settings	Nairobi, Kenya (urban), 2008, 2010-2015	1.7	2.2	10900 (UR 4600–26200)	23900 (UR 10100–57600)
	Siaya, Kenya (rural), 2011–2016	3.5			
	Nouna, Burkina Faso (rural), 2014–2016	1.5			
	Dodowa, Ghana (rural), 2011–2015	2.1			
	Manhiça, Mozambique (mixed), 2012–2016	2.8			
	Agincourt, South Africa (rural); 2010–2015	2.3			
	Mirzapur, Bangladesh (rural), 2008–2012 (Ferdous et al. 2018)	2.5			
	Multi–sites, Bangladesh (mixed), 2010–2012 (Ahmed et al. 2018)*	1.8			
Low child mortality settings	The US	1.3–1.9	1.6	2200 (UR 300–26500)	3500 (UR 500–42500)
Global estimates†					27400 (UR 10600–100000)

* Including ARI deaths identified by community survey. ARI deaths were defined as for children under 5 years, sudden onset cough or difficulty in breathing within 2 weeks of death.

† Global estimates are the sum of estimates by child mortality settings.

Table 4-6. Estimation of the attributable fraction for IFV–associated ALRI deaths for 0–59 months.*

Study country and study period	hCFRs for IFV–ALRI (%)	hCFRs for IFV–negative ALRI (%)	hCFR meta-estimate for IFV–ALRI (A)	hCFR meta-estimate for IFV–negative ALRI (B)	Ratio of case–fatality for IFV–unattributable to IFV–positive ALRI (C=B/A)	Ratio of case–fatality for IFV–attributable ALRI to IFV–positive ALRI (D, estimated using A and C)†	AF for virus–associated ALRI deaths (=AF for IFV–ALRI cases * D)‡
Togo; 2011-2013; 2014-2015	0	1.5	1.9 (0.5–6.6)	2.8 (1.2–6.5)	1.5	0.9	72%
South Africa; 1998 to 2005	4.1	5.4					
Mozambique; 2011-2014	4.3	2.6					
Gambia; 2011-2013	0	2.9					
Thailand; 2005-2011	0.1	0.2					
Morocco; 2010-2011	3.6	3.8					
Zambia; 2011-2013	19.4	17.8					
South Africa; 2011-2013	3.8	4.1					

* Studies were eligible for the analysis if they tested >=90% of cases and reported at least five ALRI deaths (to ensure the precision of estimates).

† Detailed formulas in Chapter 3.

‡ The AF for IFV–ALRI cases were calculated using odds ratios from one recent systematic reviews and two additional recent multi-country studies. The median estimate of odds ratio from the three studies was input to yield the attributable fraction for IFV–ALRI cases (80%).

Table 4-7. Estimation of the global IFV–attributable ALRI cases and deaths for children under five years

Outcome	Attributable fraction (AF, %)	Global IFV–associated burden estimates	Global IFV–attributable burden estimates*
IFV–ALRI cases (million)	80%	9.1 (UR 6.4–13.2)	7.3 (UR 5.1–10.6)
IFV–ALRI hospitalisations (*1,000)	80%	854 (UR 514–1,450)	683 (UR 411–1,160)
IFV–ALRI deaths	72%	27,400 (UR 10,600–100,000)	19,700 (UR 7,700–72,000)

* Applying the corresponding attributable fraction to the estimates of IFV–associated burden.

4.4. Conclusion and discussion

4.4.1. Implications

The IFV-associated ALRI burden estimates suggest that IFV is associated with 7% of ALRI cases, 5-17% of ALRI hospitalisations, and 3% ALRI mortality among children under five years globally (WHO 2018, McAllister et al. 2019, Troeger et al. 2018).

The hospitalisation rate of IFV-ALRI was much higher in infants than older children. A large proportion of IFV-ALRI hospitalisations (45%) and in-hospital deaths (49%) occurred during infancy, with 24% of hospitalisations and 27% of the in-hospital deaths in infants younger than six months. The estimates of IFV-ALRI hospitalisations are likely to underestimate the impact of influenza. Influenza can cause primary infections or predispose children to severe secondary bacterial infections while not being detected at specimen collection. Maternal influenza vaccination trials evaluating the vaccine efficiency against hospitalised ALRI might help understand the direct and indirect impact of influenza in causing ALRI (Nunes et al. 2017, Omer et al. 2018). Most of infant data in the analysis were from low- and middle-income countries with either no influenza immunisation policy or low influenza vaccine coverage in pregnant women during the study periods (Bangladesh, Guatemala, India, Kenya, Mozambique, South Africa, and Thailand) (Ropero-Alvarez et al. 2016, Kittikraisak et al. 2015, Lu et al. 2013). Findings from two trials in Mali and South Africa suggest that maternal influenza immunisation is an effective intervention against influenza infections in the first three months of age (Milagritos D. Tapia et al. 2016, Nunes et al. 2016). Moreover, maternal influenza immunization could reduce the burden of all-cause ALRI substantially due to influenza virus' role in predisposing individuals to secondary bacterial infections leading to severe adverse outcomes (Mina and Klugman 2014). In a pooled analysis of three maternal influenza immunization trials — conducted in South Africa, Mali,

and Nepal — there was a 20% reduction in all-cause severe clinical pneumonia in infants under six months (Omer et al. 2018).

The highest hCFRs were in LMICs, and 82% of the in-hospital deaths occurred in these countries. However, only 10% of low- and lower middle-income countries have had a national policy for influenza immunisation in children [13% for pregnant women] in 2014 (Ortiz et al. 2016). Where present there were mostly very low or unknown levels of vaccine coverage (Pan American Health Organization 2015, Members of the Western Pacific Region Global Influenza Surveillance Response et al. 2013, Palache et al. 2014, Hirve et al. 2016, Pan American Health Organization 2016). According to previous evidence, a high influenza vaccine coverage (about 70%) can substantially reduce influenza-associated hospitalisations and deaths in children under five years of age (Rolfes et al. 2019).

4.4.2. Meta-analysis results by different stratification groups

For all outcomes, the main analysis stratified by child mortality settings yielded estimates that were similar or more conservative than other stratification groups. The estimated number of IFV-episodes in the main analysis was 29% lower than the estimate in the analysis stratified by country development status (88 vs 110 million). The difference in the two estimates can be explained by the substantial variation in incidence rates between settings (e.g., developing versus industrialised countries; high child mortality versus low child mortality settings) and the different population structures in the two stratification scenarios. The global estimates of IFV-ALRI cases and hospitalisations were similar in different stratification groups. The estimate of global IFV-ALRI in-hospital deaths in the main analysis was broadly similar to the estimate in the stratified analysis by country development status, while increased by 60% in the stratified analysis by World Bank income regions (Appendix A8). The higher estimate in the analysis by World Bank income regions is mainly driven by the high hCFRs in LMICs.

4.4.3. Comparison with previous estimates

As an updated systematic review, the new estimates of incidence rates of IFV–episodes and IFV–severe ALRI for 0–59 months are generally comparable to the previous estimates for 2008 (Nair et al. 2011). However, a lower incidence rate of IFV–ALRI was estimated compared with the previous review (16 [95%CI 10–24] vs 28 [95%CI 18–44] per 1,000 children per year) for 0–59 months in developing countries. In the previous review, the incidence rate of IFV–ALRI was only based on three studies from two sites. The updated estimate was refined by incorporating data from more geographically diverse areas (12 studies) and new data with larger sample sizes achieved by multiple–season observation. Improved influenza vaccine uptake is not likely to be the reason for the lower incidence of IFV–ALRI since paediatric influenza immunization policy had not been introduced (Bangladesh, India, and Pakistan), or was only introduced in children with chronic diseases (Nicaragua); or achieved low coverage (South Africa) during the study periods (Ropero-Alvarez et al. 2016). The national PCV coverage was above 60% midway in three studies in Nicaragua, Pakistan, and South Africa. The increase in PCV uptake might contribute to the lower point value of incidence rates (International Vaccine Access Center (IVAC) and Johns Hopkins Bloomberg School of Public Health , Madhi and Klugman 2004). This explanation needs to be assessed using multi–year aggregated data in time series analysis or using individual data. The reduction in IFV–ALRI incidence rates is consistent with a general decrease in the incidence of all–cause ALRI (McAllister et al. 2019). The updated estimate of IFV–ALRI hospitalisations was similar to the previous estimate (Nair et al. 2011).

4.4.4. Long–term trend in IFV estimates, PCV introduction, and variation between years

Five studies reported annual IFV–ALRI hospitalisation rates over five years or more with PCV introduced midway in the study period (Appendix A17). The plot

showed that the trend in IFV–ALRI hospitalisation rates was inconsistent across the five studies. In the main analyses of IFV–ALRI hospitalisations most studies were from post–2009 period, and hospitalisation estimates did not change after excluding pre–2009 data (Appendix A8). In a pooled regression analysis of the five studies, no significant difference in IFV–ALRI hospitalisation rates was found between high PCV coverage period (PCV coverage >=60%) and low coverage period (<60%). However, this finding needs to be interpreted with caution because the five studies had short observation periods (5–8 years).

The annual IFV–ALRI hospitalisations rates varied across years across studies. As shown in Appendix A17, the maximum seasonal variation was 2–7–fold in four studies. The other study reported a high rate of IFV–ALRI of 1.4 per 1,000 children per year in one year while a very low rate of 0.1 per 1,000 children per year in another year. Yearly data were aggregated to ensure sufficient study sizes for age– and region–stratified analysis. However, the variation between years cannot be incorporated in the current analysis, leading to an underestimation to the uncertainties in the IFV–associated burden estimates.

It was difficult to observe or quantify any trends in hCFRs of IFV–ALRI due to the small number of IFV–ALRI deaths in multi–year studies (0–7 IFV–ALRI deaths over five or more years across nine studies).

4.4.5. Limitations related to diagnostic tests

Polymerase chain reaction (PCR) was used in 80% of studies with IFV–associated hospitalisation rates in the main analysis. Other studies used a mix of PCR and other tests (e.g., culture, immunofluorescence assays, and serologic test), immunofluorescence assays, influenza rapid test, and time-resolved fluoroimmunoassay. Immunofluorescence assays require considerable expertise, so the sensitivity can vary substantially between laboratories. The sensitivity of direct fluorescent antibody assay (DFA) can be 48–98% sensitive in detecting influenza viruses compared with molecular methods according to a

review (Landry 2011). Indirect immunofluorescence assay (IFA) can detect IFV with moderate sensitivity (70%) and high specificity (94–99%) (Iskander et al. 2009, Nutter et al. 2012). Similarly, traditional rapid influenza tests have high specificity (>90%) while low to moderate sensitivity (60–70%) for detection of IFV in children according to a systematic review (Merckx et al. 2017). These tests have low to moderate sensitivity but high specificity, thus can produce false negative results more frequently than false positive results. Therefore, the IFV–ALRI hospitalisations could have been underestimated in studies using these tests.

4.4.6. Under–detection of IFV and the adjustment for levels of testing

Not all ALRI cases were tested for IFV. Incidence and hospitalisation rates of IFV–ALRI were adjusted for the levels of testing based on the assumption that the percent positivity for IFV was the same in those tested and untested. Studies were systematically assessed, and the rates might be biased in some studies. For IFV–ALRI hospitalisation studies, rates could have been biased in 30% of studies in which less than 90% of cases were tested, and the reasons for not testing included cases being tested systematically (17%), refusal and discharge (10%), and unknown reasons (3%). Rates could have also been underestimated in 20% of studies where data on the proportion tested was unavailable. In the remaining 50% of studies, at least 90% of cases were tested. hCFRs of IFV–ALRI were not adjusted for the under–detection. hCFRs might be underestimated because children who were very ill were less likely to be sampled and tested, as suggested by the higher hCFRs among untested cases than those tested (Appendix A7).

4.4.7. Limitations related to IFV–ALRI overall mortality estimation

The IFV–ALRI overall mortality estimate for high child mortality settings was estimated using three approaches. Each approach has potential biases, and the estimate of inflation factor was based on limited data in three approaches. The

inflation factor (2.2) from the main approach (main analysis) was more conservative than the estimate from another two approaches (3.0 in Approach 2 and 4.1 in Approach 3). The estimate of mortality might be biased when generalising the results to other regions and countries, though the extrapolation was only done among countries with high child mortality. Moreover, the estimate of IFV–ALRI mortality might be biased if the percent positivity of IFV is associated with the location of child ALRI deaths (inpatient departments versus other locations, including outpatient and emergency departments, clinics, on the way to care facilities, and at home). One modelling study in South Africa estimated that a significantly higher percentage of IFV–attributable deaths occurred outside hospitals compared to the percentage of all–cause deaths occurring outside hospitals (57% versus 41%) (Cohen et al. 2018). This finding suggests that using the inflation factor for all–cause pneumonia deaths might cause an underestimation to the IFV–ALRI deaths in the main analysis. Potential biases for Approach 2 and 3 are summarised in Appendix A12.

For low child mortality settings, the inflation factor was estimated using the US data on IFV-associated mortality for 0–17 years, and was extrapolated to other regions or countries with low child mortality. The inflation factor in the US might not be generalisable to other low child mortality countries. Moreover, using data for 0–17 years might cause an underestimation if young children (i.e., under five years) are more likely to die before being admitted, or an overestimation if young children are more likely to be taken to healthcare facilities when they are sick (Noordam et al. 2015).

4.4.8. IFV–attributable burden estimates

The IFV–attributable burden estimates suggest that IFV can cause 5% of ALRI cases, 4–13% of ALRI hospitalisations, 2% of ALRI deaths among children under five years globally. The IFV–attributable mortality estimates are developed using the AF for IFV–associated deaths (72%), which was modelled by

assuming the hCFR for IFV–unattributable cases was equal to the hCFR for IFV–negative cases. The assumption might not be true, and the estimates of AF and IFV–attributable mortality could be biased. No evidence was identified to validate the assumption. The estimate of IFV–attributable deaths in high child mortality countries using the “AF” approach was similar to the estimate using the proportion of IFV–attributable ALRI deaths derived from CHAMPS data (20,100 using CHAMPS data versus 19,700 using modelled AF).

4.4.9. Comparison with estimates from other studies

Table 4–8 shows recent estimates of global IFV–associated or IFV–attributable burden among children under five years in other studies. The number of IFV–attributable ALRI cases (about 8 million) estimated by the Institute for Health Metrics and Evaluation (IHME) is generally comparable to the estimate in the main analysis (Troeger et al. 2019).

Two other studies estimated the global number of IFV–associated or IFV–attributable ALRI hospitalisations in children under five years using a proportion–based approach. IHME estimated much greater IFV–attributable ALRI hospitalisations for 2017 (about 2,200,000) compared with the estimate in the present analysis (Troeger et al. 2019). The difference in the two estimates might reflect the difference in analytical methods; data used in the two analytical methods were not directly comparable (hospitalisation rate versus proportion). In contrast, though using a proportion–based approach, the estimate of hospitalisations by Lafond and colleagues was similar to the present estimate (Lafond et al. 2016).

IFV–associated or IFV–attributable overall mortality was estimated in two studies recently published. The estimate of IFV–associated ALRI overall mortality in the present review was lower than the IFV–associated respiratory mortality estimate by Iuliano and colleagues [44,888 (95% credible interval 9,243–105,690) in 2015] for 92 countries where 92% of respiratory deaths

occurred (Iuliano et al. 2018). Iuliano and colleagues performed a time series analysis using vital respiratory deaths records and influenza circulation data in three countries, and extrapolated to other countries. The different estimates reflected the difference in case definitions (respiratory deaths versus ALRI deaths) and in statistical models (Li et al. 2017). In this review, the number of IFV–ALRI overall deaths was modelled using three different approaches, and the most conservative estimate was reported. IHME modelled an estimate of IFV–attributable ALRI overall mortality that is broadly similar to the estimate in the present analysis (about 23,400 IFV–attributable ALRI deaths in 2017) (Troeger et al. 2019).

Table 4-8. Recent estimates of global IFV–associated and IFV–attributable burden among children under five years.

	IFV estimates for 2018 in this thesis	IFV–associated ALRI hospitalisations for 2012 by Lafond and colleagues (Lafond et al. 2016)	IFV–associated respiratory mortality estimates for 2015 by Iuliano and colleagues (Iuliano et al. 2018)*	IFV – attributable burden estimates by the Institute for Health Metrics and Evaluation (IHME) for 2017 (Troeger et al. 2019)
IFV–associated ALRI hospitalisations	854,000 (UR 514,000–1,450,000)	870,000 (95% CI 610,000–1,237,000)	..	..
IFV–associated ALRI mortality	27,400 (UR 10,600–100,000)	..	44,888 (95% credible interval 9,243–105,690)	..
IFV–attributable ALRI cases	7.3 million (UR 5.1–10.6)	..	..	About 8 million (results were presented in figures)
IFV–attributable ALRI hospitalisations	683,000 (UR 411,000–1,160,000)	..	..	About 2,200,000 (results were presented in figures)
IFV–attributable ALRI deaths	19,700 (UR 7,700–72,000)	..	..	About 23,400 (results were presented in figures)

* The estimates are for 92 countries where 92% of respiratory deaths occurred. ..=not available.

4.4.10. Influenza vaccine use in children and pregnant women

Influenza vaccine use has substantially increased over the last decade in some countries (e.g., the US) (Palache et al. 2014). Inclusion of data from the low vaccine-coverage period could cause an overestimation to the estimates of IFV-ALRI cases and hospitalisations. Influenza vaccine use was not adjusted for when estimating IFV-associated burden due to the scarcity of influenza vaccine coverage data in most countries. Progress has been made to account for influenza vaccine use when estimating influenza burden at the country level (Kostova et al. 2013). Adjusting for the vaccine use at global level is challenging because the influenza vaccine coverage among children and pregnant women remains unknown in many countries, except in high-income countries such as the US and UK, and in Latin American countries (Palache et al. 2014, Pan American Health Organization 2015, European Centre for Disease Prevention and Control 2017). Another challenge is that the protective effect of influenza vaccines is dependent on the type of vaccine and the degree of match between the vaccine and circulating influenza strains, thus can vary by seasons (Osterholm et al. 2012, Manzoli et al. 2012). The coverage and the effect of administrated influenza vaccines over different seasons among different populations are required to adjust for the vaccine use at the global level.

Chapter 5 Global burden of human metapneumovirus (hMPV)–associated ALRI

5.1. Summary

Background

hMPV, first identified in 2001, is an important virus in children with ALRI, and the attributable fraction ranges from 73% to 91% according to one recent systematic review and two multi–country studies. Previous serological studies and laboratory–confirmed studies reveal that the almost all children have been exposed to or infected with hMPV by the age of five years, and children in this age group are most likely to have severe infections. Available pooled analyses of data from different populations have focused on broad age groups and showed that hMPV is associated with 6.1–6.4% of ALRI among paediatric patients under 20 years worldwide. Incidence and mortality of hMPV–ALRI are less available in published literature, especially for narrow age groups. No global or regional burden estimates have been made for children under five years.

Standardised analysis

The regional and global burden of hMPV–associated ALRI in children under five years were estimated using data from a systematic review of studies and additional high–quality unpublished studies. A generalised linear mixed model was used to combine incidence rates, hospitalisation rates, and hCFRs of hMPV–ALRI. The hMPV–ALRI cases and hospitalisations were estimated by applying the pooled incidence and hospitalisation rates to 2018 population estimates. The hMPV–ALRI in–hospital deaths were estimated by combining hospitalisations and pooled hCFRs of hMPV–ALRI. Analysis was stratified by severity, region, and age. In the main analysis, global estimates were the sum of estimates by age and by child mortality settings. The hMPV–ALRI overall mortality was estimated using the in–hospital deaths and a multiplier (“inflation

factor"). As presented in Chapter 3, to estimate the inflation factor in high child mortality settings, input data were the number of all–cause pneumonia deaths among children under five years in defined catchment areas by locations of death. For low child mortality settings, the input data were the percent of children with pneumonia seeking care per country as measured in Demographic and Health Surveys, Multiple Indicator Cluster Surveys, and other national surveys (as presented in the standardised method chapter). The data are available in UNICEF databases (Murray and Newby 2012).

The hMPV–attributable burden was estimated using hMPV–associated burden estimates and the attributable fraction (AF) for hMPV–associated cases, which was obtained from one recent systematic review and two recent multi–country studies, and the AF for hMPV–associated deaths, which was modelled using the AF for hMPV cases and data from the current systematic review. A sensitivity analysis for the hMPV–attributable burden was conducted using the proportion of hMPV–attributable ALRI deaths derived using CHAMPS data. Any adaptions to the standardised methods are presented below.

Objective

To estimate the global number of cases, hospitalisations, and deaths from hMPV–ALRI in children under five years in 2018.

5.2. Adaptation in the methods

5.2.1. Adaptation in data source – systematic review

The literature search was limited to the time points between 1 January 1995 and 31 December 2017.

5.2.2. Adaptation in statistical analysis

Hospitalisations of hMPV–associated ALRI

In addition to the incidence–based approach, the range of hMPV–associated ALRI hospitalisations was estimated using the proportion–based approach: the proportion of hMPV–ALRI, which was estimated using data from the systematic review, was applied to the hospitalisations of all–cause ALRI among children under five years. The global all–cause ALRI hospitalisations for 2015–2016 ranged from 5,133,000 to 16,400,000 among children under five years, and were used in the proportion–based approach (Troeger et al. 2018, McAllister et al. 2019). In light of the substantial differences between the two estimates of global all–cause ALRI hospitalisations, the proportion–based approach was only used to estimate the possible range for hMPV–ALRI hospitalisations (similarly for hPIV).

Overall mortality of hMPV–associated ALRI

In the main analysis, the standardised approach was used to estimate the overall hMPV–ALRI mortality. As mentioned in Chapter 4, mortality associated with certain viruses (e.g., IFV and RSV) can be modelled with population–based pneumonia deaths and local concurrent virus circulation data. This was, however, challenging for hMPV and hPIV as location–matched pneumonia mortality data and virus circulation data were more limited for the two viruses than for IFV or RSV.

Therefore, a different approach was developed for hMPV and hPIV, and the overall hMPV–ALRI mortality was estimated by applying the percent of hMPV in ALRI deaths to the number of overall ALRI deaths for children under five years, as shown in Figure 5–1.

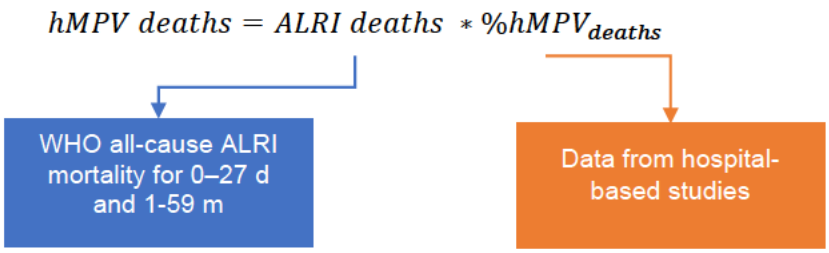

Figure 5-1. A schematic figure showing the sensitivity analysis for overall hMPV–ALRI mortality

The number of ALRI deaths were obtained from WHO mortality and global health estimates (WHO 2018). Data on ALRI mortality were available until 2017, so the 2017 estimates were used. The percent of hMPV in ALRI deaths was estimated using data from hospital–based studies in which at least 90% of ALRI cases were tested, and at least five ALRI deaths were reported. It was assumed that the percent of hMPV in ALRI deaths was the same for the hospital and the community setting. About 19% of ALRI deaths in children under five years occur in the neonatal period (WHO 2018). Thus, the percent of hMPV positives in ALRI deaths was estimated separately for 0–27 days and 1–59 months where available, and was applied to the ALRI mortality for the corresponding age group.

5.3. Results

Figure 5–2 shows the study selection for the systematic review on hMPV. Overall, 160 studies were identified with data on hMPV–ALRI community incidence rates (10 studies), hospitalisation rates (39 studies), hospitalised proportion positives (117 studies), and hCFRs (73 studies). Of these studies, 44 were unpublished studies from the collaboration network and 116 studies from published literature. By World Bank income regions, 7 studies were from LICs, 40 from LMICs, 64 from UMICs, and 49 from HICs. A summary of included studies for each outcome are in appendix (A18). Details of included studies are in Appendix A19.

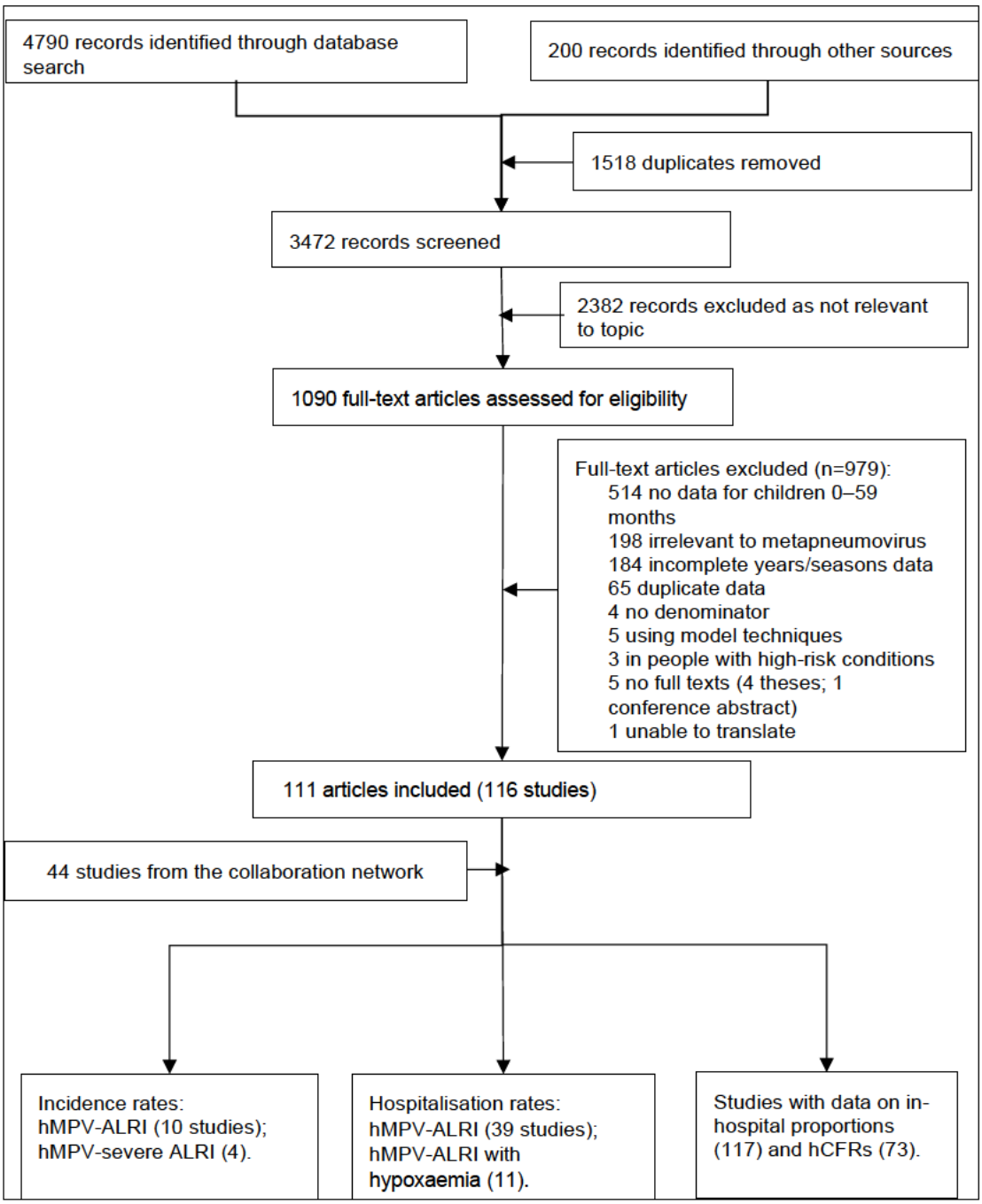

Figure 5-2. Flow diagram for selection of studies for human metapneumovirus

For multi–site papers, the site–specific data were extracted where available and were analysed as one study; in this way 116 studies were extracted from 111 papers. One study could provide data on multiple outcomes in the same population, so the total number of studies was greater than the sum of studies by outcomes.

5.3.1. hMPV-associated ALRI burden in the community

The incidence rate of hMPV-associated ALRI and the number of cases

There were 10 studies with data on the incidence of hMPV–ALRI. The incidence rates for 0–59 months were available in nine studies after imputation and these studies were included in the meta-analysis. The nine studies were from Australia (two studies), Bangladesh, India, Nepal, Pakistan, Peru, South Africa, and the US. The remaining one study reported an incidence rate of 36.5 per 1,000 children per year among American Indian children aged 24–59 months in 2009. Five studies were from high child mortality settings. By World Bank income regions, there were four studies from LMICs, two studies from UMICs, and three studies from HICs. Three studies reported the rates for pre-2010 period. For this outcome, no potentially influential studies (considerably affecting the combined estimates) were identified.

The hMPV–ALRI incidence rate meta-estimate was 21.2 (95%CI 17.1–26.2) per 1,000 children per year for 0–59 months in high child mortality settings, and 22.3 (95%CI 12.3–40.6) for low child mortality settings. The incidence rate in low child mortality settings was estimated based on three studies (one from the US and the other two from Australia), and the high rate was mainly driven by two Australian studies (one for 1996–1999 and the other one for 2010–2014). Based on the meta-estimates, 14.6 million (UR 10.5-21.0) hMPV-ALRI cases were estimated to occur globally in children under five years (Table 5–1).

In the sensitivity analysis, hMPV–ALRI incidence rate meta–estimates ranged from 17.7 (95%CI 9.9–31.8) to 27.4 (95%CI 14.6–51.3) for 0–59 months when stratified by country development status and by World Bank income groups. The global number of hMPV–ALRI cases for children under five years was 13.7 million (UR 10.1–18.9) and 13.7 million (UR 9.4–20.3) in the stratified analysis by country development status and by World Bank income groups, respectively (Appendix A9).

The number of hMPV-associated severe ALRI cases

Only four studies were identified with data on incidence rates of hMPV–severe ALRI (Appendix A9 and A19). The four studies reported incidence rates from 2011 onwards in four countries with high child mortality (Bangladesh, India, Pakistan, and South Africa). Details of the four studies are in Appendix A19. For 0–59 months, high incidence rates (17–18 per 1,000 children per year) were reported in two studies in India and South Africa, while low rates (1–2 per 1,000 children per year) in the other two studies in Bangladesh and Pakistan. The meta–estimate was 5.3 (95%CI 1.6–17.9) per 1,000 children, translating to 2.4 million (UR 0.7–7.9) hMPV–severe ALRI cases in high child mortality settings (Appendix A9).

Table 5-1. Estimates of the incidence rate (per 1,000 children per year) and the number of hMPV-associated ALRI cases among children under five years in 2018, by World Bank income regions and child mortality settings.

		LMICs	UMICs	HICs	Low child mortality (L)	High child mortality (H)	Global (L+H)*
0–5 m	No. of studies	4	1	0	0	5	
	Rate†	19.0 (5.1–67.7)	··	··	··	25.3 (8.9–69.8)	
	Cases (*1,000)	841 (233–3045)	··	··	··	1164 (418–3244)	··
6–11 m	No. of studies	4	1	0	0	5	
	Rate	22.9 (11–47)	··	··	··	26.4 (15.5–44.6)	
	Cases (*1,000)	1005 (488–2070)	··	··	··	1204 (712–2038)	··
12–59 m	No. of studies	3	1	0	0	4	
	Rate	23.4 (14.8–36.8)	··	··	··	20.6 (13.8–30.8)	
	Cases (*1,000)	8026 (5103–12626)	··	··	··	7347 (4929–10954)	··
0–59 m‡	No. of studies§	4 (1)	2 (1)	3 (2)	4 (3)	5 (1)	
	Rate	20.1 (15.5–26.1)	17.7 (9.9–31.8)	27.4 (14.6–51.3)	22.3 (12.3–40.6)	21.2 (17.1–26.2)	
	Cases (*1,000)	8669 (6690–11235)	3253 (1821–5812)	1737 (931–3241)	5123 (2826–9292)	9487 (7671–11735)	14610 (10497–21027)

* Global estimates are the sum of estimates by child mortality settings. ··=not available.
† Rates per 1,000 children per year, derived from meta–analysis.
‡ Estimates for 0–59 m are calculated by applying rates for 0–59 m to the population estimates.
§ Numbers in parenthesis are imputed studies. Rates were imputed using multiple imputation method.

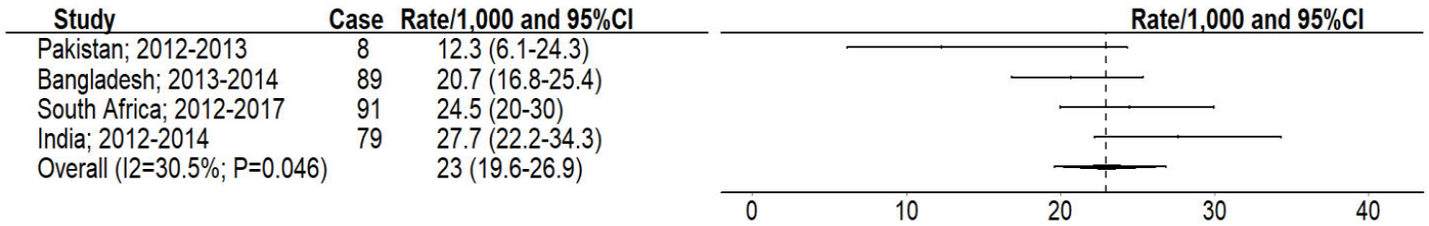

Figure 5-3. Forest plot of non–imputed incidence rates of hMPV–ALRI for children aged 0 – 59 months in high child mortality settings.

Imputed data were not included in this plot because using the multiple imputation method, a group of values were imputed for each study. Data for low child mortality settings were not plotted because there was only one study with data for 0–59 months.

5.3.2. hMPV-associated ALRI burden in the hospital setting

Hospitalisation rates of hMPV-ALRI and hospitalisations

There were 39 studies with data on hMPV–ALRI hospitalisation rates, including 29 studies with data by three narrow age bands. As shown in Figure 5–5, Figure 5–6, and Figure 5–7, the hospitalisation rates ranged from 0 to 18.0 (95%CI 9.4–34.3) per 1,000 children per years for 0–5 months, 0.9 (95%CI 0.2–3.7) to 10.9 (95%CI 4.9–24.0) for 6–11 months, and 0.1 (95%CI 0–0.6) to 2.1 (95%CI 1.7–2.5) for 12–59 months across studies. More details of included studies are in Appendix A19. When reported by age groups, estimates of two studies (in Kenya and South Africa) were potential outliers, but the estimates were not influential (significantly affecting the combined estimates). For 12–59 months, one such outlier was conducted in two refugee camps in Kenya. Compared with two other Kenyan studies with data on hMPV–ALRI hospitalisation rates for 0–59 months, this study reported a rate between the highest and lowest rate. For infants, the other such outlier was conducted in Pearl, South Africa. Some of the results from this study have already been published. In this study, individually recorded person-time at risk during the follow–up were used to estimate hospitalisation rates of hMPV–ALRI.

The pooled hospitalisation rate point estimate was more than 4–fold higher in infants aged 0–5 months and 6–11 months (2.2–3.3 per 1,000 children per year) compared to children aged 12–59 months (0.3–0.6 per 1,000 children per year) across World Bank income regions and child mortality settings (Table 5–2). The analysis stratified by child mortality settings yielded 643,000 (UR 425,000–977,000) hMPV–ALRI hospitalisations globally among children under five years. The global hospitalisations for hMPV–ALRI for children under five years only changed marginally, ranging from 626,000 to 650,000 in the stratified analysis by World Bank income regions and country development status (Appendix A9).

A total of 117 studies were identified with data on proportions of hospitalised ALRI cases positive for hMPV, including 78 studies with data for 0–59 months. For 0–59 months, the proportions ranged from 0.9 percent (95%CI 0.1–6.3) to 19.7 percent (95%CI 12.3–30.2) across the 78 studies. Meta-analyses for children aged 0–59 months showed that 5.6–6.5% of ALRI was associated with hMPV across World Bank income regions (Appendix A11). As mentioned above in this chapter, two recent estimates of global all–cause ALRI hospitalisations are very different (5,133,000 and 16,400,000), making it difficult to yield a point estimate for hMPV–ALRI hospitalisations using the proportion–based approach. The global hMPV–ALRI hospitalisations were estimated to range from 298,000 to 951,000 among children under five years using the proportion–based approach.

Hospitalisations of hMPV–ALRI with hypoxaemia

There were 11 studies with data on hospitalisation rates for hMPV–ALRI with hypoxaemia by three narrow age bands (Appendix A19). Only three studies were from the low child mortality setting. In the analysis stratified by child mortality settings, 112,000 (UR 29,000–522,000) hospitalisations for hMPV–ALRI with hypoxaemia were estimated to occur in children under five years globally, accounting for 17% of hMPV–ALRI hospitalisations (Table 5–2).

Table 5-2. Hospitalisation rates (per 1,000 children per year) and hospitalisations of hMPV–associated ALRI in children under five years in 2018, by World Bank income regions and child mortality settings.*

		LMICs	UMICs	HICs	Low child mortality (L)	High child mortality (H)	Global (L+H)†
hMPV–ALRI							
0–5 m (A)	No. of studies	8	6	5	7	12	
	Rate‡	2.4 (1.6–3.5)	3.3 (1.6–7.1)	3.3 (2.2–5.1)	2.7 (1.8–4)	3.0 (1.9–4.9)	
	Hospital admissions (*1,000)	106 (72–157)	61 (29–128)	21 (14–32)	62 (42–93)	138 (86–221)	200 (128–314)
6–11 m (B)	No. of studies	7	5	4	5	11	
	Rate	2.7 (1.7–4.3)	2.5 (1–5.9)	2.8 (2.2–3.5)	2.2 (1.5–3.4)	2.7 (1.7–4.4)	
	Hospital admissions (*1,000)	119 (75–188)	46 (19–111)	18 (14–22)	51 (34–76)	123 (77–198)	174 (110–274)
12–59 m (C)	No. of studies	9	8	5	7	15	
	Rate	0.6 (0.3–1)	0.4 (0.2–0.8)	0.3 (0.2–0.7)	0.3 (0.2–0.5)	0.6 (0.4–0.8)	
	Hospital admissions (*1,000)	206 (113–375)	59 (29–117)	15 (8–28)	55 (35–87)	214 (152–302)	269 (187–389)
0–59 m (A+B+C)§	Hospital admissions (*1,000)	431 (260–720)	165 (77–356)	54 (36–83)	168 (110–255)	475 (315–721)	643 (425–977)
hMPV–ALRI with hypoxaemia							
0–5 m (D)	No. of studies	6	3	1	2	8	
	Rate	0.3 (0–2.1)	1.3 (0.3–5.4)	··	0.6 (0.2–1.5)	0.7 (0.2–2.5)	
	Hospital admissions (*1,000)	13 (1–268)	24 (6–101)	··	14 (5–38)	32 (9–113)	46 (14–151)
6–11 m (E)	No. of studies	6	3	1	2	8	
	Rate	0.4 (0.1–2)	0.3 (0.1–1.2)	··	0.3 (0.1–1.7)	0.5 (0.2–1.7)	
	Hospital admissions (*1,000)	18 (4–78)	6 (2–19)	··	7 (2–28)	23 (8–66)	30 (10–94)
12–59 m (F)	No. of studies	6	4	1	3	8	
	Rate	0.1 (0–0.2)	0.1 (0–0.7)	··	0 (0–0.1)	0.1 (0–0.3)	
	Hospital admissions (*1,000)	34 (5–215)	15 (1–171)	··	1 (0–4)	36 (5–273)	37 (5–277)
0–59 m (D+E+F)	Hospital admissions (*1,000)	65 (10–560)	44 (9–291)	··	22 (7–70)	91 (22–452)	112 (29–522)

* Meta-analyses were only done when there were two or more studies. ··: not available.
† Global estimates by age strata are the sum of estimates by child mortality settings; global estimates for 0–59 m are the sum of estimates by age groups and child mortality settings.
‡ Rates per 1,000 children per year, derived from the meta–analysis.
§ Estimates for 0–59 m are the sum of estimates by three age groups.

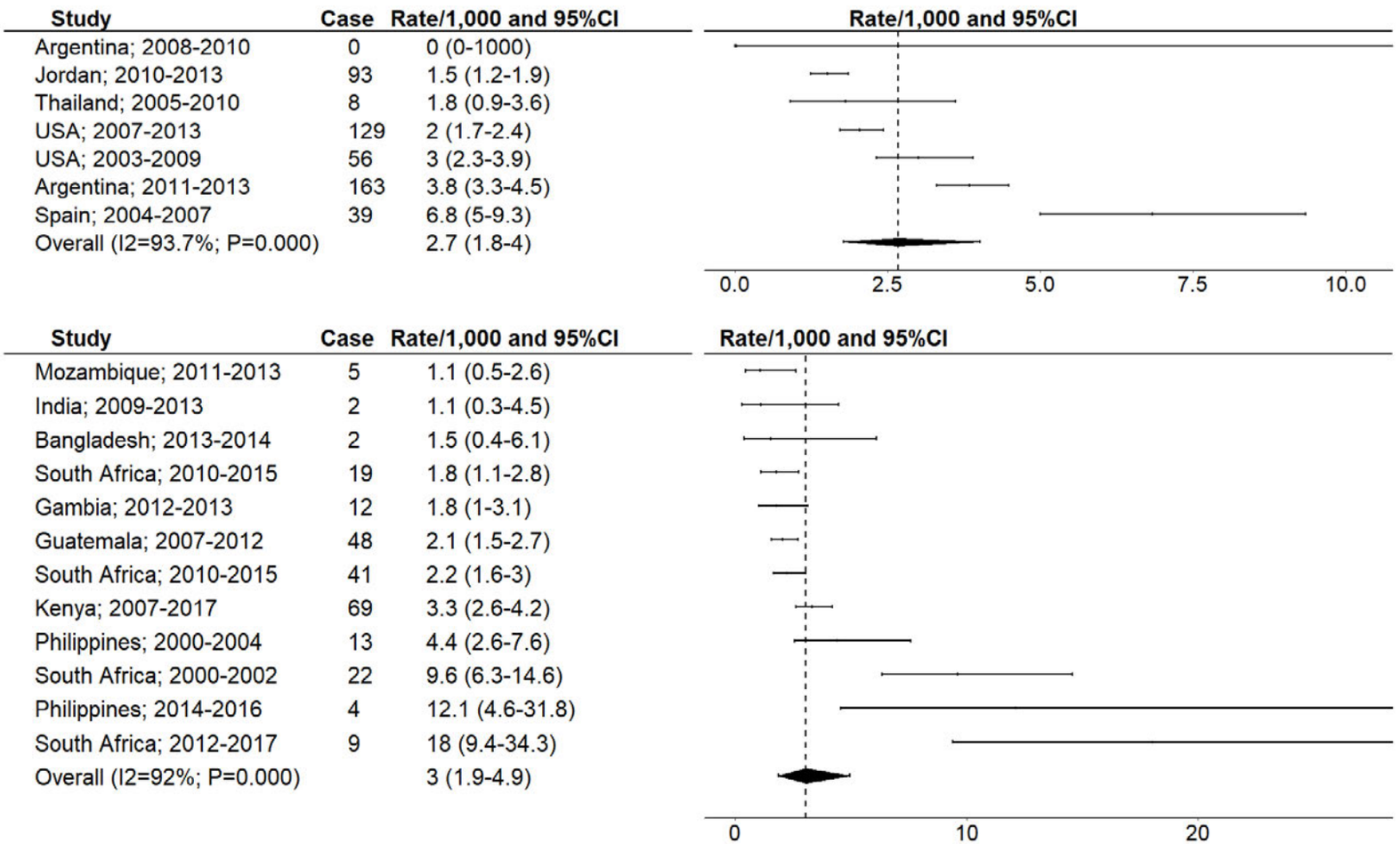

Figure 5-4. Forest plot of hospitalisation rates of hMPV–ALRI for children aged 0–5 months by child mortality settings.

Upper: low child mortality settings. Below: high child mortality settings.

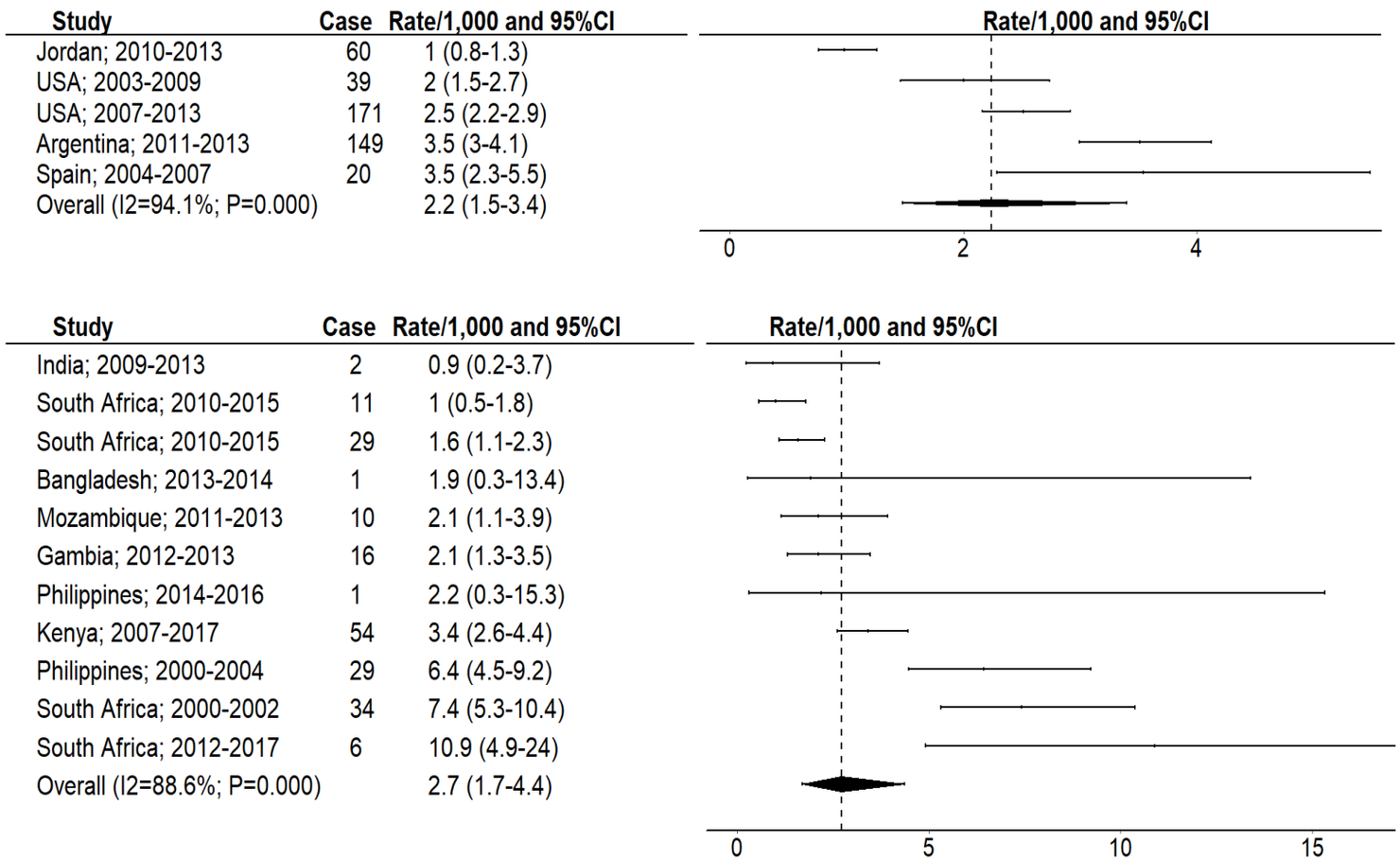

Figure 5-5. Forest plot of hospitalisation rates of hMPV–ALRI for children aged 6–11 months by child mortality settings.

Upper: low child mortality settings. Below: high child mortality settings.

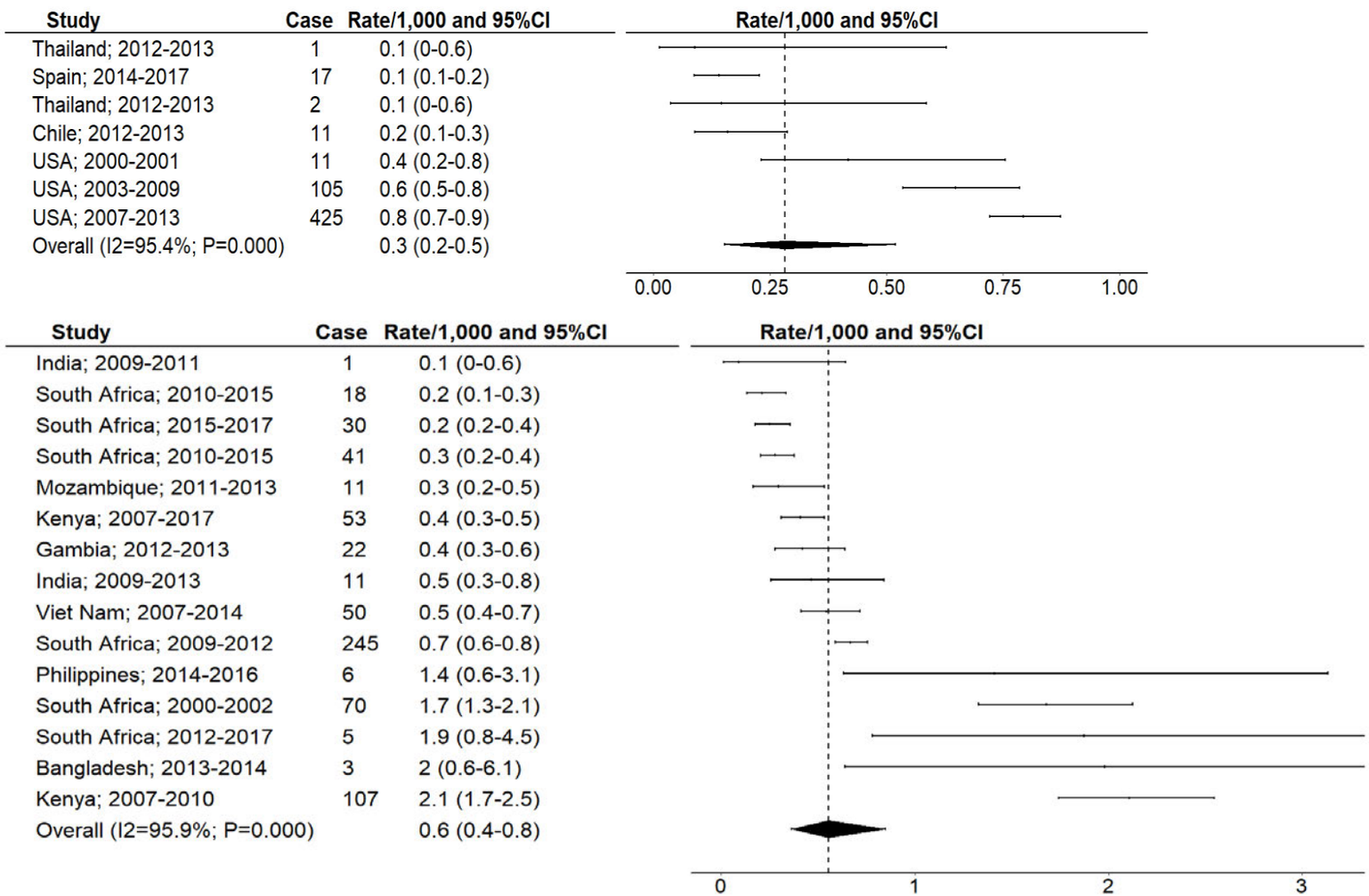

Figure 5-6. Forest plot of hospitalisation rates of hMPV–ALRI for children aged 12–59 months by child mortality settings.

Upper: low child mortality settings. Below: high child mortality settings.

hCFRs and in–hospital mortality of hMPV–associated ALRI

A total of 73 studies reported hCFRs of hMPV–ALRI in children under five years, including 28 studies with data stratified by three narrow age bands. Table 5–4 shows the studies included in the main analysis. More details are in Appendix A19. According to the meta-estimates, infants aged 0–5 months from the high child mortality setting and LMICs had highest hCFRs [4.5% (95%CI 2.3–8.6) for LMICs; 3.3% (95%CI 1.7–6.1) for high child mortality settings] (Table 5–3). The hCFRs were lower for children aged 6–59 months and for children in HICs (0.5–1.1%), with wide confidence intervals. These meta–estimates yielded 7,700 (UR 2,600–48,800) hMPV–ALRI in–hospital deaths globally in children under five years. About 64% of these deaths were in young infants aged 0–5 months [4,900 (UR 2,100–19,300)], and 88% [6,800 (UR 2,500–27,100)] occurred in countries with high child mortality. An estimated 7,200 (UR 2,600–52,300) in–hospital deaths occurred in LMICs. The estimate in the main analysis was similar to that in the stratified analysis by country development status (7,500). In the stratified analysis by World Bank income regions the estimate of global in–hospital deaths was 9100 (UR 2,900–68,800) (Appendix A9).

Table 5-3. In–hospital case–fatality ratio (hCFR) meta–estimates of hMPV–associated ALRI and in–hospital deaths in children under five years in 2018, by World Bank income regions and child mortality settings.

		LMICs	UMICs	HICs	Low child mortality (L)	High child mortality (H)	Global (L+H)*
	No. of studies	15	6	7	7	21	
0–5 m (A)	hCFR (%)†	4.5 (2.3–8.6)	1.7 (0.6–5.1)	0.4 (0–8.6)	0.4 (0–8.6)	3.3 (1.7–6.1)	
	Deaths	4300 (2000–9200)	1000 (300–3700)	100 (0–3400)	200 (0–9900)	4600 (2100–9900)	4900 (2100–19300)
6–11 m (B)	hCFR (%)	0.7 (0–9)	NA	0.6 (0.1–3.9)	0.6 (0.1–3.9)	0.2 (0–7.6)	
	Deaths	900 (0–37800)	NA‡	100 (0–700)	300 (0–1900)	200 (0–9400)	600 (100–11300)
12–59 m (C)	hCFR (%)	0.9 (0.3–2.8)	1.1 (0.1–9.1)	0.5 (0–7)	0.5 (0–7)	0.9 (0.2–3.6)	
	Deaths	1800 (500–6500)	600 (100–6600)	100 (0–2800)	300 (0–10100)	1900 (400–8300)	2200 (400–18300)
0–59 m (A+B+C)§	Deaths	7200 (2600–52300)	1700 (300–10300)	300 (0–6900)	800 (100–22200)	6800 (2500–27100)	7700 (2600–48800)

* Global estimates by age strata are the sum of estimates by child mortality settings; global estimates for 0–4 y are the sum of estimates by age and child mortality settings.
† hCFR estimates derived from the meta–analysis.
‡ All of the studies reported zero hMPV–ALRI deaths, so the hCFR for the strata was not estimated.
§ Estimates for 0–59 m are the sum of estimates by three age bands.

Table 5-4. Estimates of in–hospital case–fatality ratios (hCFRs) in individual studies included in the main analysis.

Location (Study period)	0–5 months		6–11 months		12–59 months	
	Deaths (No.)	hCFRs (%)	Deaths (No.)	hCFRs (%)	Deaths (No.)	hCFRs (%)
Seoul, Korea (2003- 2005)	0	0	0	0	1	5.6
Sør-Trøndelag County, Norway (2006-2015)	0	0	0	0	1	1
Valencia Region, Spain (2014-2017)	0	0	0	0	0	0
Berlin, Germany (2010-2014)	1	3.7	0	0	0	0
Aurora, Colorado, the US (2010-2016)	0	0	1	1.1	0	0
KFSHRC, Riyadh, Saudi Arabia (2007-2008)	0	0	0	0	2	28.6
Rabat, Morocco (2010-2011)	3	20	0	0	0	0
Taclobal, Philippines (2008-2015)	2	7.4	1	4.2	0	0
Bangladesh (2010-2014)	2	6.7	0	0	0	0
Basse, Gambia (2011-2013)	0	0	1	1.4	1	1.4
Lusaka, Zambia (2011-2014)	2	9.1	2	10.5	0	0
Bamako, Mali (2012-2014)	0	0	0	0	1	5.6
Kilifi, Kenya (2011-2013)	1	5.6	0	0	1	4.5
Karachi, Pakistan (2009-2012)	1	3.1	0	0	0	0
Soweto, South Africa (2011-2013)	0	0	0	0	2	11.8
Matlab, Bangladesh (2012-2013)	0	0	0	0	0	0
Dhaka, Bangladesh (2012-2013)	0	0	0	0	0	0
Paarl, South Africa (2012-2017)	0	0	0	0	0	0
Manhiça, Mozambique (2011)	1	20	0	0	0	0
Concepcion, Chile (2012-2013)	0	0	0	0	0	0
Pueto Princesa City, Philippines (2012-2015)	1	6.2	0	0	0	0
Kamalapur, Bangladesh (2013-2014)	0	0	0	0	0	0
Soweto, South Africa (2015-2017)	0	0	0	0	0	0

Global burden of acute lower respiratory infection (ALRI) associated with influenza virus, human metapneumovirus, and human parainfluenza virus among children under five years

Location (Study period)	0–5 months		6–11 months		12–59 months	
	Deaths (No.)	hCFRs (%)	Deaths (No.)	hCFRs (%)	Deaths (No.)	hCFRs (%)
Soweto, Gauteng, South Africa (2000-2002)	1	4.5	0	0	1	1.4
Kilifi, Kenya (2007-2017)	1	1.4	0	0	0	0
Klerksdorp, South Africa (2010-2015)	1	5.3	0	0	0	0
Pietermaritzburg, South Africa (2010-2015)	1	2.4	0	0	0	0
Naval, Philippines (2012-2016)	0	0	0	0	0	0

5.3.3. Overall mortality of hMPV–associated ALRI

Approach 1 – the "inflation factor" approach

The inflation factor for hMPV–ALRI deaths in the high child mortality setting was estimated using the same data as used for IFV–ALRI deaths (Table 5–4). More details of the data are given in Chapter 4. A median inflation factor of 2.2 across eight sites was applied to the hMPV–ALRI in–hospital deaths, yielding 14,900 (UR 5,600–59,700) overall hMPV–ALRI deaths in high child mortality settings. Across 28 countries or regions with low child mortality, 22% to 94% of children with pneumonia received care from a health provider. Using these data, the median inflation factor was estimated to be 1.3 across regions or countries, yielding 1,100 (UR 100–28,800) overall hMPV–ALRI deaths among children under five years for the low child mortality setting. Altogether, the "inflation factor" approach yielded 16,100 (UR 5,700–88,000) overall hMPV–ALRI deaths globally among children under five years (Table 5–4).

Approach 2 – the proportion of hMPV positives in ALRI deaths

hMPV was identified in 3.2% (95%CI 1.9–5.2) of ALRI deaths (573 ALRI deaths in total) for children aged 1–59 months. Details are given in Appendix A14. Using this approach, the point value of the overall hMPV–ALRI mortality for the high child mortality setting was 30% higher than the "inflation factor" approach, with overlapping confidence intervals [19,900 (UR 12,100–33,200) for 1–59 months] (Appendix A14). The overall deaths in neonates were not estimated using this approach because very few neonatal ALRI deaths were reported in hospital–based studies, and no hMPV deaths were identified.

Table 5-5. Estimation of overall hMPV–associated ALRI mortality using the "inflation factor" approach.

Setting	Site	Ratio of all pneumonia deaths over in–hospital deaths for 0–59 m (A)	Inflation factor (B=median of A)	In–hospital mortality of hMPV–ALRI (C)	Overall MPV–ALRI mortality (D=B*C)
High child mortality settings	Nairobi, Kenya (urban), 2008, 2010-2015	1.7	2.2	6,800 (UR 2,500–27,100)	14,900 (UR 5,600–59,700)
	Siaya, Kenya (rural), 2011–2016	3.5			
	Nouna, Burkina Faso (rural), 2014–2016	1.5			
	Dodowa, Ghana (rural), 2011–2015	2.1			
	Manhiça, Mozambique (mixed), 2012–2016	2.8			
	Agincourt, South Africa (rural); 2010–2015	2.3			
	Mirzapur, Bangladesh (rural), 2008–2012 (Ferdous et al. 2018)	2.5			
	Multi–sites, Bangladesh (mixed), 2010–2012 (Ahmed et al. 2018)*	1.8			
Low child mortality settings	28 countries and regions (UNICEF 2016)	Ranging from 1.1 to 4.5	1.3	800 (UR 100–22,200)	1,100 (UR 100–28,800)
Global estimates†					16,100 (UR 5,700–88,000)

* Including ARI deaths identified by community survey. ARI deaths were defined as for children under 5 years, sudden onset cough or difficulty in breathing within 2 weeks of death.

† Global estimates are the sum of estimates by child mortality settings.

5.3.4. hMPV–attributable ALRI burden estimates

Approach 1 – the attributable fraction (AF) approach

A median AF of 78% for hMPV–ALRI was used to estimate hMPV–attributable ALRI cases and hospitalisations (Appendix A15; Table 5–7). Combining the hMPV–associated burden estimates and the AF, 11.4 million (UR 8.2–16.4) ALRI cases and 502,000 (UR 332,000–762,000) ALRI hospitalisations could be attributed to hMPV in children under five years (Table 5–7).

The ratio of case–fatality of hMPV–unattributable ALRI and hMPV–attributable ALRI to that of hMPV–associated cases was estimated to be 1.4 and 0.9, respectively, based on 13 hospital–based studies. Details of this analysis are in Table 5–6. Using the ratios, the AF for hMPV–associated ALRI deaths was estimated to be 70%. This suggested that 5,400 (UR 1,800–34,100) in–hospital ALRI deaths and 11,300 (UR 4,000–61,600) overall ALRI deaths could be attributed to hMPV globally, including 10,400 (UR 3,900–41,800) for high child mortality settings (Table 5–6).

Approach 2 - proportion of hMPV-attributable ALRI deaths

The proportion of hMPV–attributable deaths in ALRI deaths was 1.6 (95%CI 0.3–4.5) in children aged 1–59 months using CHAMPS data from high child mortality countries. Accordingly, 9,900 (UR 2,600–39,300) ALRI deaths could be attributed to hMPV among children aged 1–59 months for high child mortality settings (Appendix A15). The hMPV-attributable deaths in neonates were not estimated using this approach because no hMPV-attributable deaths were identified among neonates in CHAMPS.

Table 5-6. Estimation of the attributable fraction for hMPV–associated ALRI deaths for 0–59 months.*

Study country and study period	hCFRs for hMPV–ALRI (%)	hCFRs for hMPV–negative ALRI (%)	hCFR meta-estimate for hMPV–ALRI (A)	hCFR meta-estimate for hMPV–negative ALRI (B)	Ratio of case–fatality for IFV–unattributable to hMPV–positive ALRI (C=B/A)	Ratio of case–fatality for hMPV–attributable to hMPV–positive ALRI (D, estimated using A and C)†	AF for hMPV–associated ALRI deaths (=AF for hMPV–ALRI cases * D)‡
Morocco; 2010-2011	4.3	3.8	3.2 (2.0–5.0)	4.5 (2.7–7.6)	1.4	0.9	70%
Philippines; 2008-2015	2.8	6.1					
Philippines; 2012-2015	0	4.9					
Bangladesh; 2010-2014	4.4	1.5					
Gambia; 2012-2013	2	2.8					
Zambia; 2012-2013	7.5	18.8					
Mali; 2012-2014	2.1	16.2					
Kenya; 2011-2013	3.6	4.9					
South Africa; 2011-2013	3.4	3.8					
Philippines; 2014-2016	0	5					
Mozambique; 2011-2013	3.6	1.3					
Philippines; 2012-2015	1.8	2.1					
Philippines; 2012-2016	0	2.6					

* Studies were eligible for the analysis if they tested >=90% of cases and reported at least five ALRI deaths (to ensure the precision of estimates).

† Detailed formulas in Chapter 3.

‡ The AF for hMPV–ALRI cases was calculated using odds ratios from one recent systematic reviews and two additional recent multi-country studies. The median estimate of odds ratio from the three studies was input to yield the attributable fraction for hMPV–ALRI cases (78%).

Table 5-7. Estimation of the global hMPV–attributable ALRI cases and deaths for children under five years

Outcome	Attributable fraction (AF, %)	Global hMPV–associated burden estimates	Global hMPV–attributable burden estimates*
hMPV–ALRI cases (million)	78%	14.6 (UR 10.5–21.0)	11.4 (UR 8.2–16.4)
hMPV–ALRI hospitalisations (*1,000)	78%	643 (UR 425–977)	502 (UR 332–762)
hMPV–ALRI deaths	70%	16,100 (UR 5,700–88,000)	11,300 (UR 4,000–61,600)

* Applying the corresponding attributable fraction to the estimates of hMPV–associated burden.

5.4. Conclusion and discussion

5.4.1. Implications

The hMPV–associated burden estimates suggest that hMPV is associated with 11% of ALRI cases, 4–13% of ALRI hospitalisations, and 2% of ALRI deaths among children under five years globally (WHO 2018, McAllister et al. 2019, Troeger et al. 2018).

The meta-estimate of hMPV–ALRI incidence rate did not vary much by age groups (21–26 per 1,000 children per year across 0–5 months, 6–11 months and 12–59 months), indicating that hMPV is associated with ALRI throughout early childhood. This result needs to be verified with more data. In contrast, the hospitalisation rate was much higher in infants; about 58% of hospitalisations (374,000) and 71% of in–hospital deaths (5,500) for 0– 59 months occurred in the first year of life. The substantial morbidity and mortality burden during infancy might reflect the increased susceptibility of infants to severe respiratory infections, due to the immaturity of infant's immune system (Simon et al. 2015). Additionally, the maternal antibodies against hMPV infections decay over the first several months of life, leaving infants susceptible to severe infections. Consistent with this, a follow–up study among 40 Israeli children found the prevalence of anti–hMPV antibodies declined by 50% at seven months of age compared with the prevalence at two months (Fadeela et al. 2003). Infants' hMPV–ALRI hospitalisation rate was consistently high across different settings, highlighting the need to develop safe and effective vaccines targeting hMPV to protect infants against severe hMPV infections.

The hCFR estimates of hMPV–ALRI show that younger infants aged 0–5 months are at an increased risk of hMPV–ALRI mortality. In contrast to the pattern for the hospitalisation rate, the hCFR for 0–5 months varied by settings. The variation of hCFRs by World Bank income regions could reflect the difference in hospital care and disease severity at admission. The higher hCFRs

among children in low– and lower middle–income countries could be a result of multiple factors, including the high prevalence of certain underlying conditions which can predispose children to severe infections, no access to care and delays in care–seeking which can lead to rapid deterioration, and the poor quality of hospital care (McAllister et al. 2019, Pneumonia Etiology Research for Child Health Study Group (PERCH) 2019). In this respect, further efforts are needed to improve the outcome of hMPV–ALRI in infants in low– and lower middle–income countries.

5.4.2. Meta-analysis results by different stratification groups

The global estimates for hMPV–ALRI hospitalisations and in–hospital deaths were mostly similar when stratified by different groups (Appendix A9), with one exception for hMPV-ALRI in–hospital deaths, for which outcome the point estimate increased by 18% in the stratified analysis by World Bank income regions (9,100 versus 7,700). The hospitalisation estimates (298,000–951,000; Appendix A11) derived from the proportion–based approach were broadly similar to those using an incidence–based approach. The estimates for hMPV–ALRI and severe ALRI need to be interpreted with caution due to the limited data for this outcome and the substantial variation between studies.

5.4.3. Long–term trend in hMPV estimates and variation between years

Five studies provided yearly hospitalisation rates of hMPV–ALRI over five years or more for children aged 0–59 months (Appendix A17). The yearly hMPV–ALRI hospitalisations rates appeared to follow a cyclical pattern over every 3–5 years in three studies.

No consistent secular trends in hospitalisation rates were observed across the five studies. A reduction in the hospitalisation rates was seen in two studies in Kenya and South Africa, while an increase was seen in the other three studies in South Africa, Vietnam, and Norway. The maximum decrease was seen in the

Kenyan study (1.9 per 1,000 children per year during 2007-2009 versus 0.7 during 2010-2016), while the maximum increase was seen in the Vietnamese study (0.4 per 1,000 children per year during 2007-2009 versus 0.7 during 2010-2014).

Variation between seasons were observed. The maximum seasonal variation was mostly 3–7–fold except in two studies where the number of hMPV–ALRI cases was extremely low in certain years and the rates were very imprecise. For hCFRs, six studies provided yearly data over five years or more for children aged 0–59 months. It was difficult to observe or quantify any trends in hCFRs of hMPV–ALRI because there were very few hMPV–ALRI deaths (1–3 deaths) in these multi–year studies. Similar to the analysis for IFV, the aggregation of yearly data could have caused an underestimation to the uncertainties in the hMPV–associated burden estimates.

5.4.4. Limitations related to diagnostic tests

In the main analysis, 90% of hospitalisation studies used PCR to detect hMPV. The remaining studies used indirect immunofluorescence assay (IFA), a mix of PCR and other tests (direct immunofluorescence assay [DFA], culture, and serologic test). IFA, DFA, or culture has showed lower sensitivity (38–80% for DFA; 73% for IFA; 32% for culture) and similar specificity compared to molecular tests (Ebihara et al. 2005, Jokela et al. 2010, Wolf et al. 2015, Mahony 2008). As discussed in Chapter 4, the use of these tests might lead to an underestimation to hospitalisation rates of hMPV–ALRI.

5.4.5. Under–detection of hMPV and the adjustment for levels of testing

Similar to IFV, not all the ALRI cases were tested for hMPV. Incidence rates and hospitalisation rates of hMPV were adjusted for the levels of testing based on the assumption that the percent positivity for hMPV was the same in those tested and untested. The hospitalisations of hMPV–ALRI might be biased in 31% of studies in which less than 90% of cases were tested mainly due to

refusal (17%) and systematic sampling and testing (7%), and for unknown reasons (3%). Moreover, rates might be underestimated in another 4% of studies in which the proportion tested was unavailable. hCFRs of hMPV–ALRI were not adjusted for the under–detection. Since the hCFR of the tested ALRI cases was higher than those untested, the hCFR of hMPV–ALRI and in–hospital mortality might be underestimated (Appendix A7).

5.4.6. Limitations for hMPV–ALRI overall mortality estimation

The inflation factor for high child mortality settings was estimated using the same data as used for IFV. Therefore, the hMPV–ALRI overall mortality estimate is susceptible to similar limitations as the IFV estimate, including limitations related to the scarcity of data, the extrapolation of inflation factor from data–existing regions to other regions and the validity of the assumption in the estimation of “inflation factor” . Nevertheless, the estimate of overall hMPV–ALRI mortality in high child mortality settings derived from the “inflation factor” approach is more conservative, and the point value increased by about 30% using “the proportion of hMPV in ALRI deaths” approach (Appendix A14).

For low child mortality countries, the inflation factor, estimated using the reciprocal of the percent of children with pneumonia symptoms seeking care, were likely to be underestimated. This is because the definition of “care–seeking” is broader than the definition of “in–hospital” in this thesis: contact with primary care is included as “care–seeking” in the surveys (e.g., Multiple Indicator Cluster Surveys and Demographic and Health Surveys) but are not included in the “in–hospital mortality” estimate in the present work. The US vital statistics data show that about 40% of under–five pneumonia deaths occurred in outpatient or emergency departments during 2010–2017 (Centers for Disease Control and Prevention and National Center for Health Statistics). The estimate might also be biased if the case–fatality ratio was different between those children who received care and those who did not. The direction of the bias is

hard to determine: the cases admitted into hospitals are likely to be more severe and have a higher risk of death; but the non–severe cases who do not seek care can deteriorate rapidly (Bennett et al. 2015, Najnin et al. 2011, Onyango et al. 2012). Moreover, such data (i.e., the percent of children with pneumonia seeking care) in HICs are not readily available in published reports, and extrapolating data from other low child mortality countries to HICs might have biased the estimate.

5.4.7. hMPV–attributable burden estimates

The hMPV–attributable burden estimates show that hMPV can cause 8% of ALRI cases, 3–10% of ALRI hospitalisations, and 1% of ALRI mortality in children under five years globally. The assumption of the AF approach is similar to the analysis for IFV, which is explicated in Chapter 4. The assumption will be discussed in detail in Chapter 7. The estimate in high child mortality countries using the AF approach was similar to the estimate derived using the proportion of hMPV attributable ALRI deaths from CHAMPS data (10,400 using AF versus 9,900 using CHAMPS).

Chapter 6 Global burden of human parainfluenza virus (hPIV)–associated ALRI

6.1. Summary

Background

There are four major hPIV serotypes, from hPIV–1 to hPIV–4, and the prevalence and the attributable fraction vary by types. An earlier meta–analysis of data in different populations estimated that hPIV was associated with 2.7% of hospitalised ALRI in children under five years. This estimate was only based on seven studies with a mixture of age strata (e.g., 0–23 months and 0–59 months). Over the past decade, there have been an increasing number of hospital–based studies worldwide reporting the proportion of hPIVs in childhood ALRI cases. In contrast, data on incidence rates, hospitalisation rates, and case–fatality ratios of hPIV–ALRI, which are important measures of disease or healthcare burden associated with the virus, are less available in published reports. Global burden estimates for hPIV–ALRI in children under five years have not been made.

Standardised analysis

The regional and global burden of hPIV–associated ALRI in children under five years were estimated using data from a systematic review of published literature and additional high–quality unpublished studies. As specified in the standardised methods, a generalised linear mixed model was used to combine data for each outcome. One major adaption for hPIV was that prior to meta–analysis, data were adjusted at study levels to account for the non–detection of hPIV4. Then adjusted incidence rates and hospitalisation rates and adjusted hCFRs were input to yield the number of hPIV–ALRI cases, hospitalisations, and in–hospital deaths. Details of the adaptions are presented in this chapter.

Analysis was stratified by severity, region, and age. In the main analysis, global estimates were the sum of estimates by age and by child mortality settings. The

hPIV–ALRI overall mortality was estimated using the in–hospital deaths and a multiplier ("inflation factor"). As presented in Chapter 3, to estimate the inflation factor in high child mortality settings, input data were the number of all–cause pneumonia deaths among children under five years in defined catchment areas by locations of death. For low child mortality settings, the input data were the percent of children with pneumonia seeking care per country as measured in Multiple Indicator Cluster Surveys, Demographic and Health Surveys, and other national surveys (data are available in UNICEF databases) (Murray and Newby 2012).

The hPIV–attributable burden was estimated using hPIV–associated burden estimates and the attributable fraction (AF) for hPIV–associated cases, which was estimated based on two recent multi–country studies, and the AF for hPIV–associated deaths, which was modelled using the AF for hPIV cases and data from the present systematic review. A sensitivity analysis for the hPIV–attributable burden was conducted using the proportion of hPIV–attributable ALRI deaths derived from CHAMPS data. Any adaptions to the standardised methods are presented below in this chapter.

Objective

To estimate the global number of cases, hospitalisations, and deaths from hPIV–ALRI in children under five years in 2018.

6.2. Adaptation in the methods

6.2.1. Adaptation in data source – systematic review

The literature search was limited to the time points between 1 January 1995 and 31 December 2017.

6.1.2. Adaptation in statistical analysis

Similar to hMPV, the following analysis was conducted for hPIV; details of analysis are available in the chapter of hMPV (Chapter 5 – 5.2 Adaptation in statistical analysis), so are not presented here.

- Hospitalisations of hPIV–associated ALRI were estimated using the proportion–based approach.
- The overall hPIV–associated ALRI mortality was estimated by combining the proportion of hPIV in ALRI deaths (using hospital data) and all–cause ALRI mortality.

Adjusted hospitalisations of hPIV–associated ALRI – accounting for missing hPIV–4

Only a small fraction of hospitalisation studies detected hPIV–4; studies mainly detected hPIV–1 to hPIV–3. The hPIV–ALRI hospitalisations could be underestimated due to the non–detection of hPIV–4. Therefore, the hPIV–ALRI hospitalisations were adjusted accordingly to account for the missing hPIV–4 data as shown in Figure 6–1. This adjustment requires the prevalence of hPIV types.

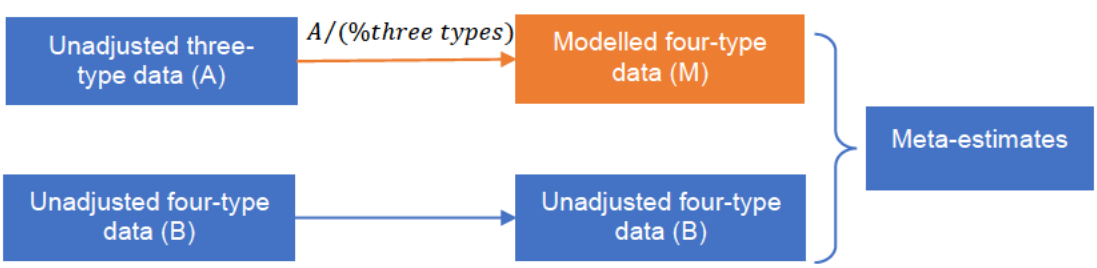

Figure 6-1. A schematic figure showing the adjustment in hospitalisations of hPIV–ALRI to account for missing hPIV–4.

The prevalence of each hPIV type

The prevalences of the four hPIV types in all hPIVs were estimated using data from the systematic review. Studies with the numbers of cases for each hPIV

type were eligible for this analysis. The analysis was restricted to hospital–based studies because the majority of the hPIV type data were from hospital-based studies. For the type analysis, the numerator was the number of cases positive for each hPIV type as they were reported. The denominator was the number of all hPIV cases as they were reported where available, otherwise was calculated accordingly in different scenarios. The primary aim was to estimate the percent of four hPIV types (especially hPIV–4) among children under five years; age–stratified analysis was not performed due to the relatively small sizes of most studies. However, age distributions could differ between types. Thus, only the four–type data for children aged 0–59 months were included in the analysis.

Adjusted hCFRs and in–hospital deaths of hPIV–associated ALRI – accounting for missing hPIV–4

Not all hCFR studies detected hPIV–4, so the hCFRs were adjusted at the study level to account for missing hPIV–4 hospitalisations and deaths using the type–specific prevalence and type–specific hCFRs. The adjustment is shown in Figure 6–2. The adjusted hCFRs (and adjusted hospitalisations) were used as input data to yield the adjusted hPIV–associated ALRI in–hospital deaths.

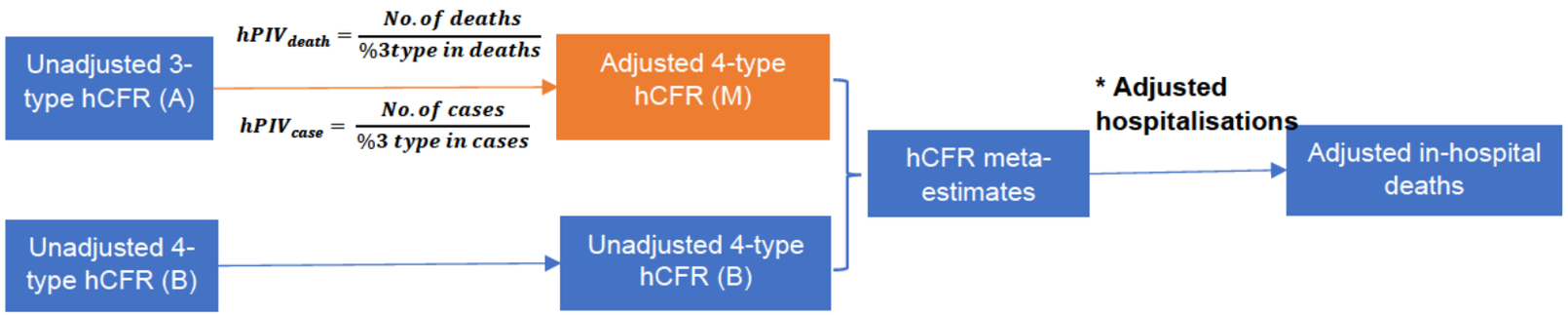

Figure 6-2. A schematic figure showing the adjustment for the missing hPIV–4 in hCFRs of hPIV–ALRI.

The prevalence of hPIV–4 in all hPIV deaths was estimated using the prevalence of four hPIV types and the ratio of case–fatality of hPIV–4 to the other three types. More details are in Appendix 13.

The hPIV–attributable ALRI mortality

Approach 1 – the "attributable fraction (AF)" approach

As mentioned in the standardised method, the hPIV–attributable burden was estimated by applying the AF to the adjusted hPIV–associated morbidity and mortality estimates. Pooled analyses of multi–country data show that the AF for hPIV–associated ALRI cases varies by type (Pneumonia Etiology Research for Child Health Study Group (PERCH) 2019, Benet et al. 2017), so the average AF in hPIV cases was estimated using type–specific AF and type–specific prevalence (Formula 6–1).

Formula 6–1: $AFEaverage = \sum_i^4 \% \, hPIVi * AFi$

In the formula, %hPIV*i* denote the prevalence of hPIV–1 to hPIV–4; AF*i* denote the AF for each type. Input data and final estimates are listed in Appendix A15.

Similar to IFV and hMPV, the AF in deaths for hPIV was estimated using the following formula:

Formula 6–2: $\mathrm{AFdeaths}\ (\%) = \mathrm{AFcases}\ (\%) * \frac{CFR(hPIVattributable)}{CFR(hPIVassociated)}$

The AFdeaths and AFcases denote the attributable fraction for hPIV–associated ALRI cases and deaths, respectively; the average AF in cases was the input for AFcases. The ratio of case–fatality of hPIV–attributable [CFR (hPIVattributable)] and hPIV–associated ALRI [CFR (hPIVassociated)] were calculated using data from 12 hospital–based studies. Data were eligible for this analysis if at least 90% of ALRI cases were tested, at least five ALRI deaths were reported, and four hPIV types were detected. More details are in Appendix A15.

Approach 2 – the proportion of hPIV–attributable ALRI deaths

As mentioned in the standardised method, the hPIV–attributable mortality was also estimated using the proportion of hPIV–attributable ALRI deaths based on

CHAMPS data (CHAMPS). Four hPIV types are detected in CHAMPS (Diaz et al. 2019).

6.2. Results

Figure 6–3 shows the study selection for hPIV. A total of 190 studies were identified with data on hPIV–ALRI community incidence (12 studies), hospitalisation rates (35 studies), hospitalised proportion positives (160 studies), and hCFRs (56 studies). There were 41 studies from the collaboration network and 149 studies from published literature. By World Bank income regions, 7 studies were from LICs, 35 from LMICs, 102 from UMICs, and 46 from HICs. Figure 6–4 shows the location of included studies. A summary of included studies for each outcome are in appendix (A18). Details of included studies are in Appendix A19.

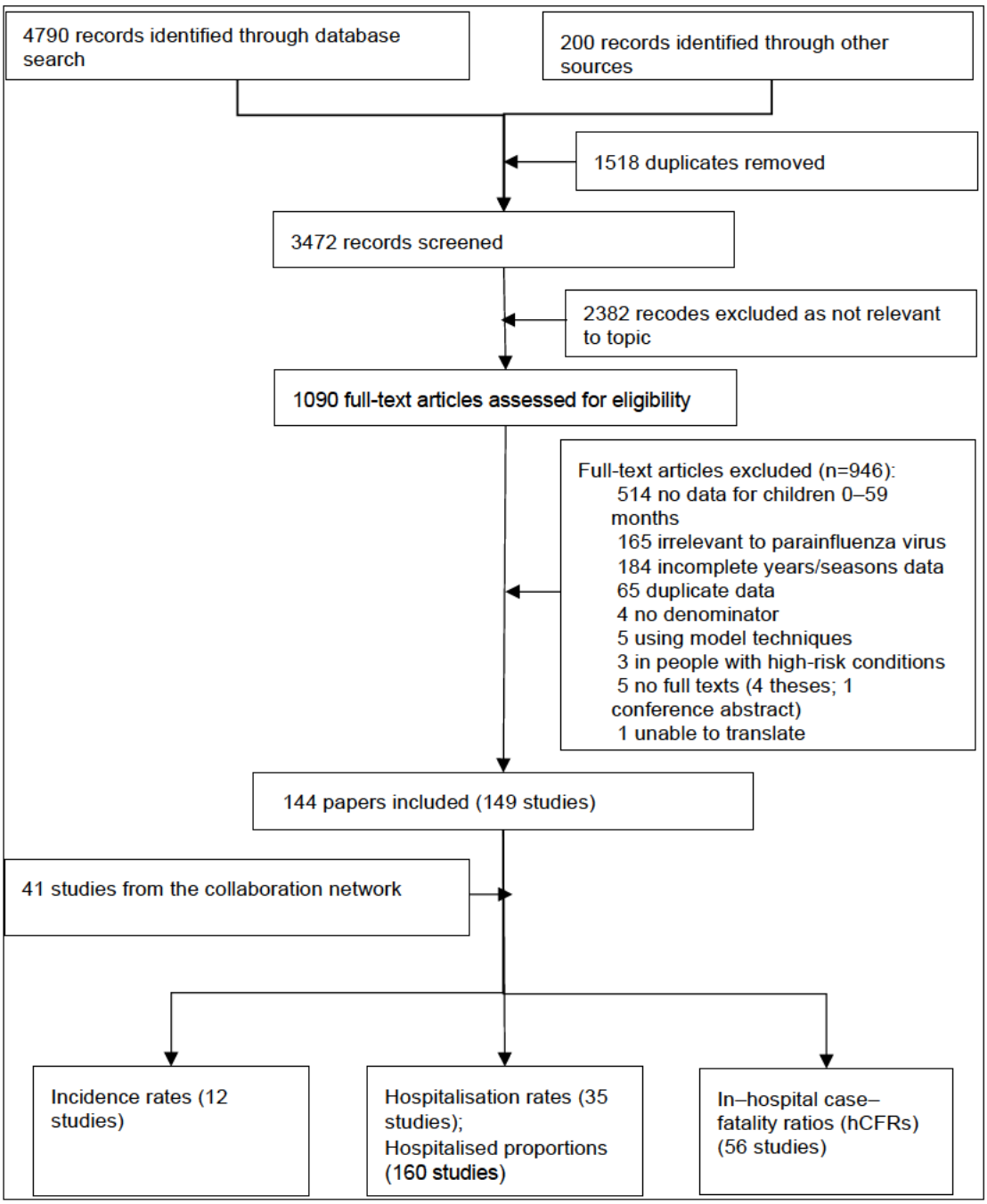

Figure 6-3. Flow diagram for study selection for human parainfluenza virus

For multi–site papers, the site–specific data were extracted where available and were analysed as one study; in this way 149 studies were extracted from 144 papers. One study could provide data on multiple outcomes in the same population, so the total number of studies was greater than the sum of studies by outcomes.

6.2.1. hPIV–associated burden in the community

The number of hPIV–associated ALRI cases

There were 12 studies with data on incidence rates of hPIV–ALRI cases, including 11 studies with data for 0–59 months (including imputed data). Seven studies were from high child mortality countries, including five from South–East Asia and the other one from South Africa. Four studies were from low child mortality countries, including two from Australia, one from Spain, and one from the US. Six studies reported the rates for pre–2010 period. One study detected four hPIV types, one study only detected hPIV–3, and other studies detected hPIV–1 to hPIV–3. Four older studies used test methods that are less sensitive than PCR: ELISA, DFA, conventional culture, and culture with IFA. No influential studies (significantly affecting the combined estimates) were found for this outcome.

The adjusted hPIV–ALRI incidence rate meta–estimate was 42.5 (95%CI 31.2–57.8) per 1,000 children per year for 0–59 months for high child mortality settings, and 45.5 (95%CI 22.7–91.0) for low child mortality settings. The high incidence rate in low child mortality settings was mainly driven by two Australian studies (one for 1996–1999 and the other for 2010–2014). Based on the meta–estimates, 29.5 million (UR 19.2–46.7) hPIV–ALRI cases were estimated to occur globally in children under five years (Table 6–1). Similar hPIV–ALRI incidence rate meta–estimates for 0–59 months (42–46 per 1,000 children per year) were estimated by country development status, by World Bank income regions, and by child mortality settings. The number of hPIV–ALRI cases were not estimated in UMICs because there was only one study. In the stratified analyses by country development status, 29.0 (UR 20.6–41.4) million hPIV–ALRI cases were estimated to occur globally among children under five years (Appendix A10).

The number of hPIV–associated severe ALRI cases

There were only five studies with data on incidence rates of hPIV–associated severe ALRI cases, all of which were from high child mortality countries. For children aged 0–59 months, the unadjusted rate of hPIV–severe ALRI ranged from 2 to 30 per 1,000 children per year for 0–59 months across five studies. The lowest rate was reported in a Bangladeshi study and the highest rate in a South African study. The meta–estimate was 9.3 (3.5–24.9) per 1,000 children per year, yielding 4.2 (UR 1.6–11.1) hPIV–severe ALRI cases in high child mortality settings (Appendix A10).

Table 6-1. Estimates of the adjusted incidence (per 1,000 children per year) and adjusted number of hPIV–associated ALRI cases in the community in children under five years in 2018, by World Bank income regions and child mortality settings*

		LMICs	UMICs	HICs	Low child mortality (L)	High child mortality (H)	Global (L+H)
0–5 m	Study†	4	1	0	0	5	
	Rate	28 (10.9–69.8)	..	..	..	36.8 (15.9–82.5)	
	Cases (*1,000)	1240 (493–3123)	..	..	..	1694 (747–3843)	..
6–11 m	Study	4	1	0	0	5	
	Rate	82.9 (66.6–102.7)	..	..	..	80 (66.4–96.1)	
	Cases (*1,000)	3639 (2934–4514)	..	..	..	3651 (3038–4388)	..
12–59 m	Study	3	1	0	0	4	
	Rate	34.4 (17.8–65.4)	..	..	..	32.9 (20–53.6)	
	Cases (*1,000)	11797 (6177–22539)	..	..	..	11733 (7188–19161)	..
0–59 m	Study	6 (3)	1	4 (3)	4 (3)	7 (3)	
	Rate	41.7 (28.6–60.7)	..	45.5 (22.7–91)	45.5 (22.7–91.0)	42.5 (31.2–57.8)	
	Cases (*1,000)	17964 (12347–26144)	..	2882 (1445–5750)	10432 (5231–20816)	19045 (14009–25897)	29478 (19240–46714)

* The incidence rate was adjusted to account for the missing hPIV–4 (in 9 studies). In one study only the hPIV–3 rate was available, so the rate was adjusted to account for the missing hPIV–1, hPIV–2, and hPIV–4. For the remaining one study, four types were detected so the rate was not adjusted.
† No of studies. The number in the parentheses were the number of imputed studies. Rates were imputed using multiple imputation method.

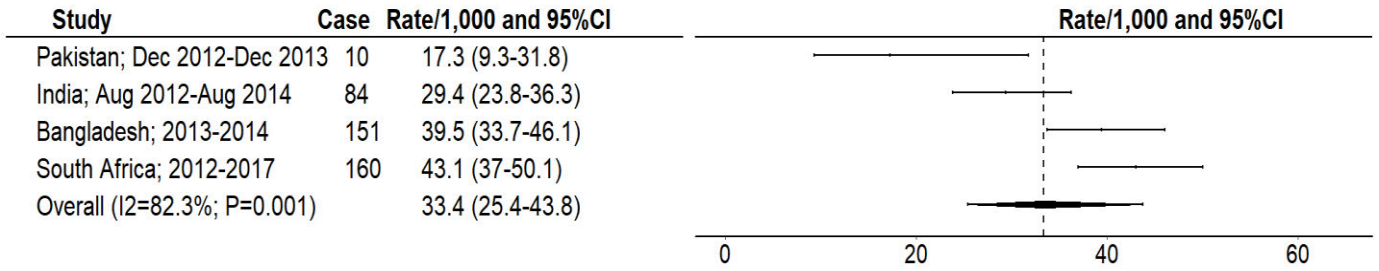

Figure 6-4. Forest plot of incidence rates of hPIV–ALRI for children aged 0–59 months in high child mortality settings.

Imputed data were not included in this plot because a group of values were imputed for each study using the multiple imputation approach. Data from low child mortality settings were not plotted because there was only one study with data (non-imputed) for 0–59 months. The pooed incidence rate point estimate in high child mortality settings increased after imputation. This rate was mainly driven by three studies in Bangladesh (39.5 per 1,000 children per year for 0–59 m), South Africa (43.1 per 1,000 children per year for 0–59 m), and Nepal (48 per 1,000 children per year for 0–23 m) reporting high rates. The three studies had the largest sample sizes. After imputation, the rates for 0–59 m in the Nepali study were included in the meta–analysis.

6.2.2. hPIV–associated burden in the hospital setting

Adjusted hospitalisations of hPIV–ALRI

There were 35 studies with hPIV–ALRI hospitalisation rates, including 26 studies reporting data by three narrow age groups. Only 9 studies detected four hPIV types. More details of included studies are in Appendix A19. hPIV-4 accounted for 12% of all hPIV cases among children under five years (Appendix A13). After adjusting for missing hPIV-4 at the study level, as shown in Figure 6–5, Figure 6–6, and Figure 6–7 (Above), the hospitalisation rates of hPIV–ALRI ranged from 0.8 to 30.1 (95%CI 18.2–49.3) per 1,000 children per years for 0–5 months, 0.6 (95%CI 0.4–0.8) to 18.1 (95%CI 9.8–33.4) for 6–11 months, and 0 to 6.8 (5.3–8.7) for 12–59 months across studies. The adjusted hospitalisation rate meta–estimate was 2–8–fold higher in infants aged 0–5 months and 6–11 months (2.0–5.8 per 1,000 children per year) compared to children aged 12–59 months (0.7–0.8 per 1,000 children per year) across World Bank income regions and child mortality settings (Table 6–2). In the analysis by child mortality settings, 1.0 million (UR 0.6–1.8) hPIV–ALRI hospitalisations were estimated to occur globally in children under five years. The global hospitalisations of hPIV–ALRI in children under five years ranged from 969,000 to 1.0 million across different stratification groups (Appendix A10).

There were 160 studies with data on proportions of hospitalised ALRI cases positive for hPIV, including 91 studies with data for 0–59 months. hPIV was positive in 8.7% of hospitalised ALRI in children aged 0–59 months, ranging from 6.7% to 11.1% across World Bank income regions (Appendix A11). Using the proportion–based approach, 447,000–1,427,000 ALRI hospitalisations were associated with hPIVs among children under five years globally. As discussed in Chapter 5, it was difficult to give a point estimate using the proportion–based approach because of the substantial differences between the two input estimates for global all–cause ALRI hospitalisations.

Adjusted hospitalisations of hPIV–ALRI with hypoxaemia

There were 13 studies with data on hospitalisation rates for hPIV–ALRI with hypoxaemia by age strata. Five studies did not detect hPIV–4. In the analysis stratified by child mortality settings, 166,000 (UR 94,000–795,000) hospitalisations (adjusted) for hPIV–ALRI with hypoxaemia were estimated to occur in children aged 0–59 months globally, accounting for 16.5% of the hPIV–ALRI hospitalisations.

Table 6-2. Adjusted hospitalisation rates (per 1,000 children per year) and adjusted hospitalisations of hPIV–associated ALRI in children under five years by World Bank income regions and child mortality settings. *†

		LMICs	UMICs	HICs	Low child mortality (L)	High child mortality (H)	Global (L+H)
hPIV–ALRI							
0–5 m (A)	No. of studies	7	6	4	7	10	
	Rate (/1,000)	3.8 (1.8–7.8)	5.7 (3–10.5)	5.5 (3.1–9.9)	3.6 (1.8–7)	5.8 (3.7–9.2)	
	Hospitalisations (*1,000)	168 (81–349)	105 (56–196)	35 (20–62)	83 (42–163)	267 (170–420)	350 (212–583)
6–11 m (B)	No. of studies	7	5	3	5	10	
	Rate (/1,000)	3.5 (1.7–7)	3.8 (1.9–7.6)	3.5 (1.9–6.5)	2 (0.9–4.6)	4.7 (3.2–6.7)	
	Hospitalisations (*1,000)	154 (76–311)	70 (35–139)	22 (12–41)	46 (20–104)	214 (149–310)	260 (169–413)
12–59 m (C)	No. of studies	8	8	4	8	12	
	Rate (/1,000)	0.8 (0.4–1.4)	0.8 (0.4–1.6)	0.8 (0.2–2.9)	0.8 (0.3–1.9)	0.7 (0.5–1.2)	
	Hospitalisations (*1,000)	274 (147–512)	117 (59–233)	41 (11–153)	147 (59–368)	250 (162–386)	396 (220–753)
0–59 m (A+B+C)	Hospitalisations (*1,000)	596 (304–1171)	292 (150–569)	98 (42–257)	276 (121–634)	731 (480–1116)	1007 (601–1750)
hPIV–ALRI with hypoxaemia							
0–5 m (D)	No. of studies	6	3	1	2	7	
	Rate (/1,000)	0.7 (0.3–1.6)	1.9 (1.1–3.1)	..	0.2 (0.1–0.3)	1.4 (0.9–2.4)	
	Hospitalisations (*1,000)	31 (13–71)	35 (21–59)	..	5 (3–8)	64 (40–105)	69 (42–113)
6–11 m (E)	No. of studies	6	3	1	2	7	
	Rate (/1,000)	0.4 (0.1–0.9)	1.1 (0.6–1.9)	..	0.1 (0.1–0.2)	0.9 (0.5–1.5)	
	Hospitalisations (*1,000)	18 (6–52)	20 (11–36)	..	2 (2–3)	41 (24–71)	43 (25–74)
12–59 m (F)	No. of studies	6	6	1	4	8	

* Rates were adjusted to account for missing hPIV–4.
† Global estimates for each age group were the sum of estimates by region. Regional estimates for 0–59 months were the sum of estimates by age groups. Global estimates for 0–59 months were the sum of estimates by age and region.

Global burden of acute lower respiratory infection (ALRI) associated with influenza virus, human metapneumovirus, and human parainfluenza virus among children under five years

		LMICs	UMICs	HICs	Low child mortality (L)	High child mortality (H)	Global (L+H)
	Rate (/1,000)	0.1 (0.1–0.2)	0.1 (0–1.3)	··	0.1 (0–4.8)	0.1 (0.1–0.2)	
	Hospitalisations (*1,000)	34 (24–48)	15 (1–232)	··	18 (1–558)	36 (25–50)	54 (26–608)
0–59 m (D+E+F)	Hospitalisations (*1,000)	65 (10–560)	44 (9–291)	··	25 (5–569)	141 (89–226)	166 (94–795)

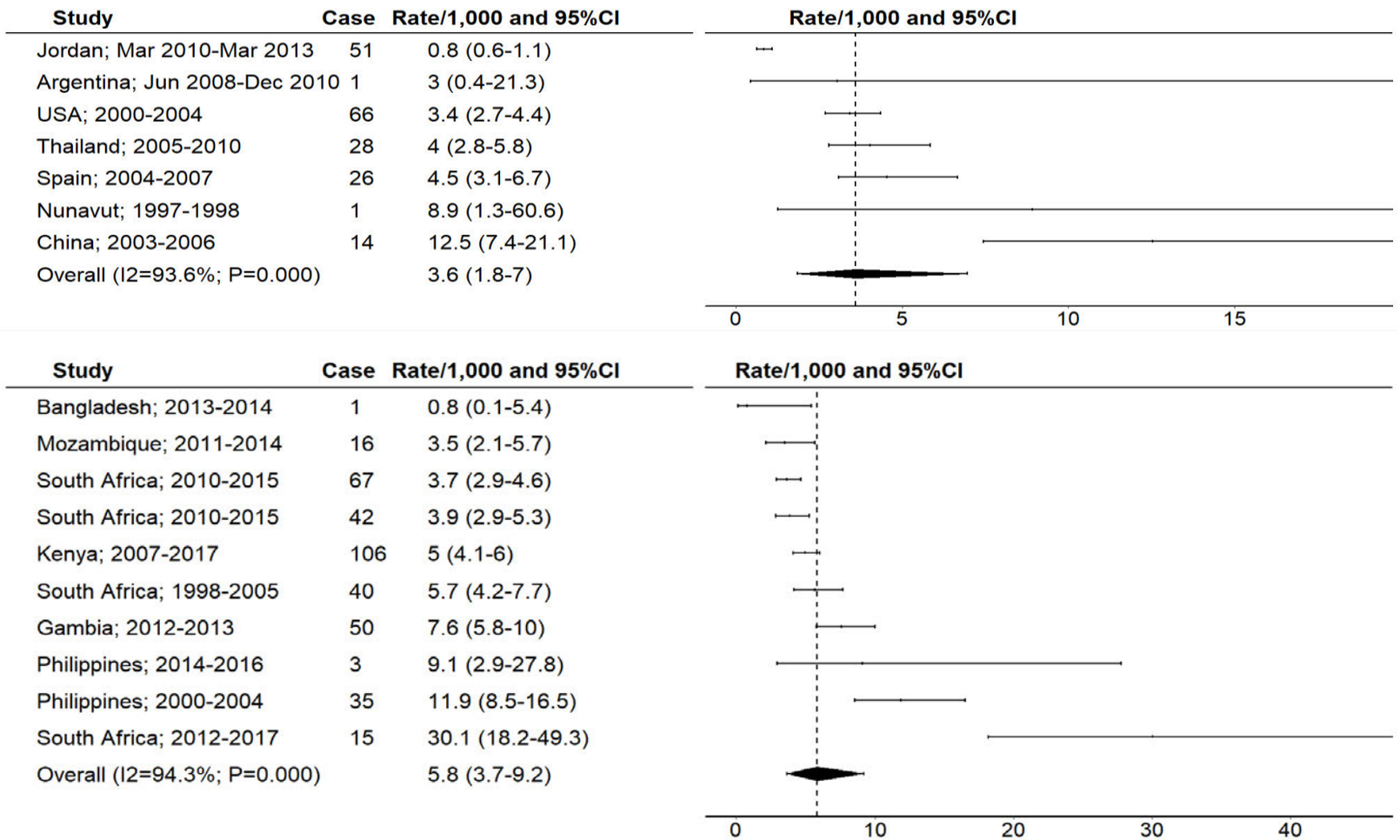

Figure 6-5. Forest plot of adjusted hospitalisation rates of hPIV–ALRI for children aged 0–5 months by child mortality settings.

Upper: low child mortality settings. Below: high child mortality settings.

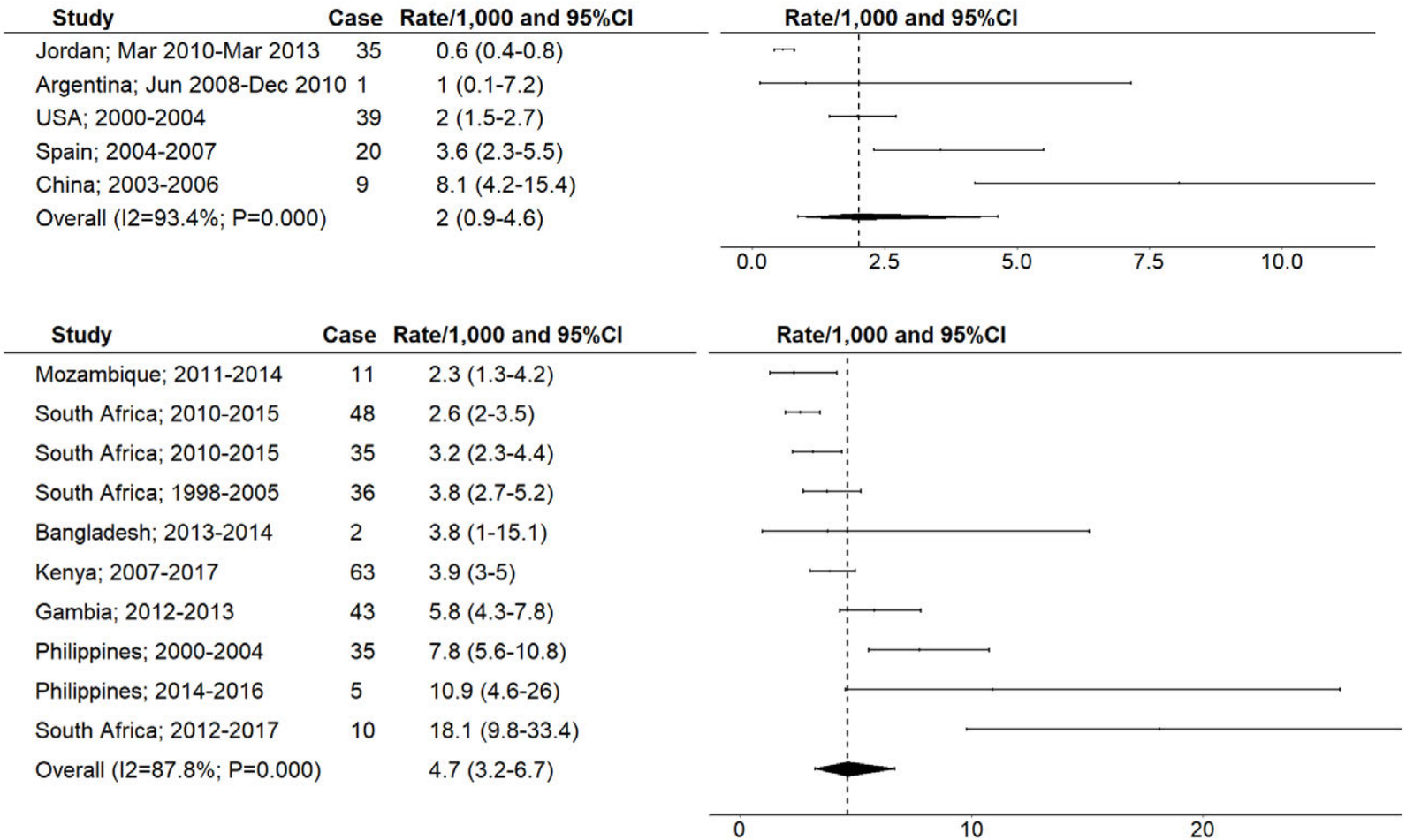

Figure 6-6. Forest plot of adjusted hospitalisation rates of hPIV–ALRI for children aged 6–11 months by child mortality settings.

Upper: low child mortality settings. Below: high child mortality settings.

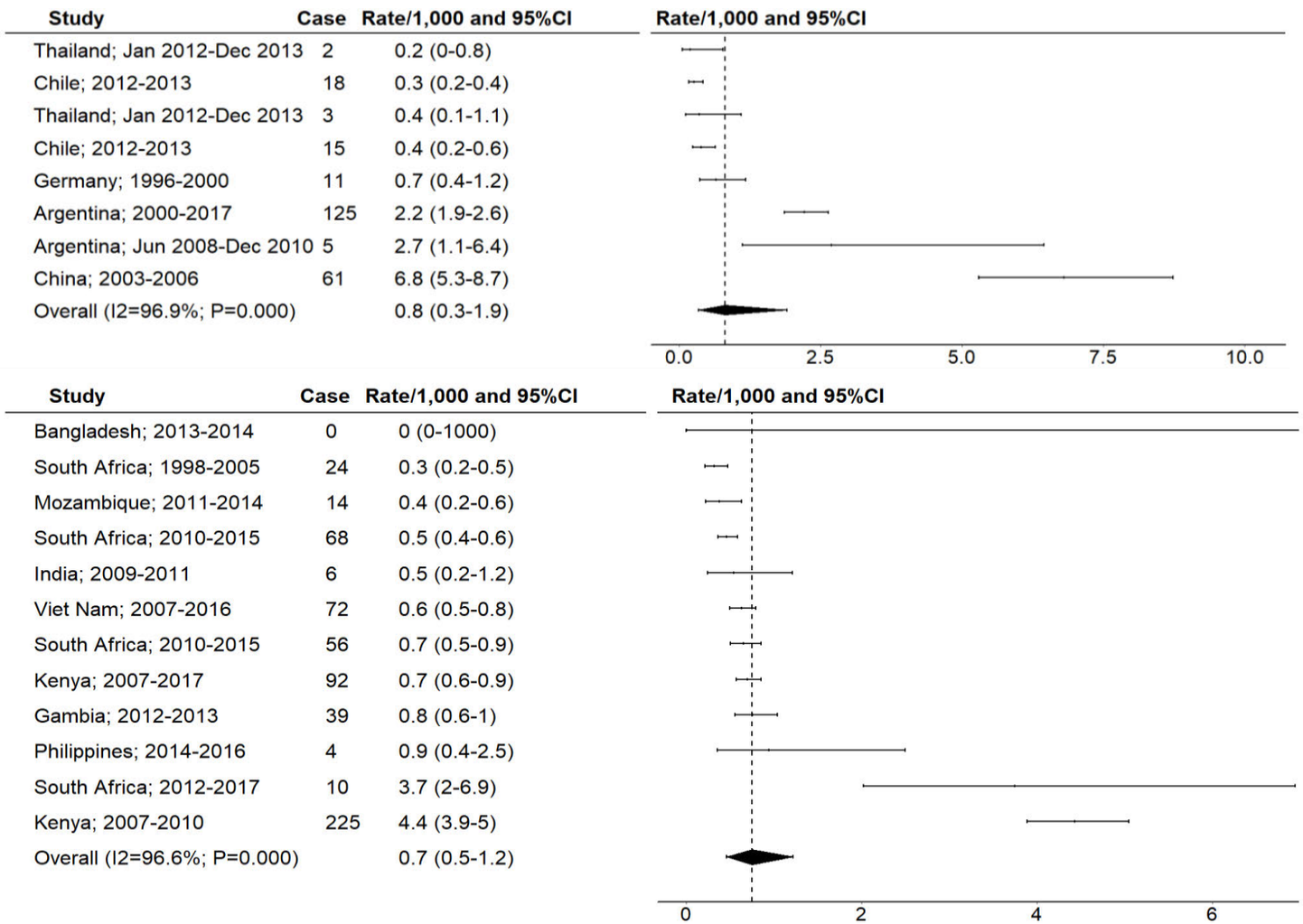

Figure 6-7. Forest plot of adjusted hospitalisation rates of hPIV–ALRI for children aged 12–59 months by child mortality settings.

Upper: low child mortality settings. Below: high child mortality settings.

Adjusted hCFRs and in–hospital mortality of hPIV–associated ALRI

There were 56 studies with data on hCFRs for hPIV–ALRI in children under five years, including 27 studies with data stratified by three narrow age bands. In eight studies hPIV–4 was not detected. Table 6–4 shows the age–stratified hCFR estimates. More details are in Appendix A19. A 1–2–fold difference was found in the hCFR meta-estimates between age groups for each setting. Children in high child mortality countries and those in LMICs generally had the highest hCFRs (2.3–3.6% across three age groups for high child mortality settings; 2.0–3.9% for LMICs) (Table 6–3). Based on these meta–estimates, 25,700 (UR 12,000–56,500) hPIV–ALRI in–hospital deaths were estimated to occur among children under five years. About 42%, 24%, and 34% of these deaths were in children aged 0–5 months, 6–11 months, and 12–59 months, respectively. In LMICs, there were 19,400 (UR 7,800–50,800) hPIV–ALRI in–hospital deaths among children under five years. In the stratified analysis by World Bank income regions, the global in–hospital deaths were estimated to be 27,800 (UR 11,000–73,700) (Appendix A10).

Table 6-3. Adjusted in–hospital case–fatality ratio (hCFR) meta–estimates of hPIV–associated ALRI and adjusted in–hospital deaths in children under five years, by World Bank income regions and child mortality settings.*†

		LMICs	UMICs	HICs	Low child mortality (L)	High child mortality (H)	Global (L+H)
	No. of studies	15	8	4	7	20	
0–5 m (A)	hCFR (%)	3.9 (2.1–7.3)	2.4 (1.3–4.6)	0.9 (0.2–3.6)	1.3 (0.6–3.1)	3.6 (2.2–5.8)	
	Deaths	6600 (2600–17000)	2500 (1100–6100)	300 (100–1500)	1100 (400–3100)	9600 (5000–18600)	10700 (5400–21700)
6–11 m (B)	hCFR (%)	2 (0.5–7.4)	3.8 (2.2–6.6)	1.2 (0.3–4.7)	2.6 (1–6.9)	2.3 (0.9–5.8)	
	Deaths	3100 (700–13800)	2700 (1100–6400)	300 (100–1200)	1200 (300–4200)	4900 (1800–13300)	6100 (2200–17300)
12–59 m (C)	hCFR (%)	3.5 (2.2–5.6)	1.9 (0.8–4.1)	0.9 (0.4–1.9)	1.2 (0.7–2.3)	2.8 (1.8–4.4)	
	Deaths	9600 (4500–20900)	2200 (800–6400)	400 (100–1700)	1800 (600–5200)	7000 (3800–13000)	8800 (4400–18100)
0–59 m (A+B+C)	Deaths	19400 (7800–50800)	7400 (3000–18900)	1000 (200–4100)	4100 (1400–12400)	21600 (10600–44100)	25700 (12000–56500)

* The in-hospital deaths were estimated using adjusted hospitalisations and adjusted hCFRs to account for the missing hPIV-4.
† Global estimates for each age group were the sum of estimates by region. Regional estimates for 0–59 months were the sum of estimates by age groups. Global estimates for 0–59 months were the sum of estimates by age and region.

Table 6-4. Estimates of in–hospital case–fatality ratios (hCFRs) in individual studies included in the main analysis.

Location (study period)	0–5 months		6–11 months		12–59 months	
	Deaths (No.)	hCFRs (%)	Deaths (No.)	hCFRs (%)	Deaths (No.)	hCFRs (%)
Kawayan and Caibiran, Philippines (2014-2016)	0	0	0	0	0	0
Naval, Philippines (2012-2016)	0	0	0	0	0	0
Muntinlupa, Philippines (2012-2015)	1	100	0	0	0	0
Ospital ng Palawan, Philippines (2012-2015)	0	0	0	0	1	5
Kilifi, Kenya (2007-2017)	2	2.4	1	2	3	4.5
Buenos Aires, Argentina (2008-2010)	0	0	0	0	0	0
multiple areas, Bangladesh (2010-2014)	0	0	0	0	0	0
Matlab, Bangladesh (2012-2013)	0	0	0	0	0	0
Basse, Gambia (2012-2013)	1	2	1	2.3	1	2.6
Lusaka, Zambia (2011-2014)	2	7.7	3	12.5	2	11.8
Nakhon Phanom, Thailand (2012-2013)	0	0	0	0	0	0
Soweto, South Africa (2011-2013)	2	4.3	3	9.1	0	0
Dhaka, Bangladesh (2012-2013)	0	0	0	0	0	0
Kilifi, Kenya (2011-2011)	1	5.9	0	0	1	2.9
Bamako, Mali (2012-2014)	2	5.1	6	18.8	3	10.3
Rabat, Morocco (2010-2011)	2	9.5	0	0	4	3.4
Buenos Aires, Argentina (2000-2017)	3	2.1	7	5.2	4	3.6
Manhiça, Mozambique (2011-2014)	0	0	0	0	0	0
Iquique, Chile (2012-2013)	0	0	0	0	0	0
Concepcion, Chile (2012-2013)	0	0	0	0	0	0
Soweto, South Africa (1998-2005)	2	5.7	1	3.1	0	0
Paarl, South Africa (2012-2017)	1	7.7	0	0	0	0
Klerksdorp, South Africa (2010-2015)	0	0	1	3.2	1	2

Global burden of acute lower respiratory infection (ALRI) associated with influenza virus, human metapneumovirus, and human parainfluenza virus among children under five years

Location (study period)	0–5 months		6–11 months		12–59 months	
	Deaths (No.)	hCFRs (%)	Deaths (No.)	hCFRs (%)	Deaths (No.)	hCFRs (%)
Pietermaritzburg, South Africa (2010-2015)	1	1.7	0	0	1	1.7
Colorado, United States of America (2010-2016)	1	0.8	2	1.9	6	1.2
Berlin, Germany (2010-2014)	1	1.9	0	0	0	0
Taclobal City, Philippines (2008-2015)	4	14.3	1	4.2	1	3.7

6.2.3. Overall mortality of hPIV–associated ALRI

The hPIV–ALRI overall mortality was estimated using the same inflation factors as used in the analysis for hMPV: an inflation factor of 2.2 was used for high child mortality settings and 1.3 for low child mortality settings. Details of the estimation of inflation factors are in Chapter 5 – 5.2 Adaptions in the methods. Using the “inflation factor” approach, 53,000 (UR 25,300–113,500) overall hPIV–ALRI deaths were estimated to occur globally in children under five years, including 47,600 (UR 23,400–97,100) deaths in high child mortality settings and 5,300 (UR 1,800–16,200) in low child mortality settings (Table 6–4). In the sensitivity analysis for high child mortality settings, hPIV was positive in 7.3% (95%CI 4.6–11.3) of ALRI deaths (584 ALRI deaths in total) for 0–59 months. Based on this percent, 56,100 (UR 36,500–87,400) overall hPIV–ALRI deaths were estimated to occur in children under five years in high child mortality settings (Appendix A14).

Table 6-5. Estimation of overall hPIV–ALRI mortality using the "inflation factor" approach.*

Setting	Site	Ratio of all pneumonia deaths over in–hospital deaths for 0–59 months (A)	Inflation factor (B=median of A)	In–hospital mortality of hPIV–ALRI (C)	Overall hPIV–ALRI mortality (D=B*C)
High child mortality settings	Nairobi, Kenya (urban), 2008, 2010-2015	1.7	2.2	21600 (10600–44100)	47600 (UR 23400–97100)
	Siaya, Kenya (rural), 2011–2016	3.5			
	Nouna, Burkina Faso (rural), 2014–2016	1.5			
	Dodowa, Ghana (rural), 2011–2015	2.1			
	Manhiça, Mozambique (mixed), 2012–2016	2.8			
	Agincourt, South Africa (rural); 2010–2015	2.3			
	Mirzapur, Bangladesh (rural), 2008–2012(Ferdous et al. 2018)	2.5			
	Multi–sites, Bangladesh (mixed), 2010–2012(Ahmed et al. 2018)†	1.8			
Low child mortality settings	28 countries and regions (UNICEF 2016)	Ranging from 1.1 to 4.5	1.3	4100 (1400–12400)	5,300 (UR 1,800–16,200)
Global estimates‡					53000 (UR 25300–113500)

* Datasets for inflation factor estimation are the same as those used for hMPV analysis.
† Including ARI deaths identified by community survey. ARI deaths were defined as for children under five years, sudden onset cough or difficulty in breathing within two weeks of death.
‡ Global estimates are the sum of estimates by child mortality settings.

6.2.4. hPIV–attributable burden estimates

Based on type-specific prevalence and AF, an average AF of 73% was estimated for hPIV–associated ALRI cases and 66% for hPIV–associated ALRI deaths among children under five years (Appendix A15; Table 6–6). Based on the AFs and hPIV–associated burden estimates, 21.5 million (UR 14.0–34.1) ALRI cases, 735,000 (UR 439,000–1,277,000) ALRI hospitalisations, 17,000 (UR 7,900–37,300) in–hospital ALRI deaths, and 35,000 (UR 16,700–74,900) could be attributed to hPIV in children under five years globally (Table 6–6). Based on CHAMPS data, hPIVs were detected in 2.2% (95%CI 0.3–7.7) of ALRI deaths in neonates and 6.8% (95%CI 3.7–11.4) for 1–59 months. Applying the proportions to the estimates of all–cause ALRI mortality, 45,500 (UR 24,900–91,700) ALRI deaths could be attributed to hPIV among children under five years in high child mortality settings (Appendix A16).

Table 6-6. Estimation of the attributable fraction for hPIV–associated ALRI deaths for 0–59 months. *

Study country and study period	hCFRs for hPIV–ALRI (%)	hCFRs for hPIV–negative ALRI (%)	hCFR meta–estimate for hPIV–ALRI (A)	hCFR meta–estimate for hPIV–negative ALRI (B)	Ratio of case–fatality for IFV–unattributable to hPIV–positive ALRI (C=B/A)	Ratio of case–fatality for hPIV–attributable to hPIV–positive ALRI (D, estimated using A and C)†	AF for hPIV–associated ALRI deaths (=AF for hPIV–ALRI cases * D)‡
Philippines; 2014–2016	0	5.4	4.1 (2.3–6.9)	4.8 (3.2–7.3)	1.2	0.9	66%
Philippines; 2012–2016	0	2.6					
Philippines; 2012–2015	33.3	5.1					
Philippines; 2012–2015	3	2.1					
Gambia; 2012–2013	2.3	2.9					
Zambia; 2011 – 2014	10.4	18.7					
South Africa; 2011–2013	4.5	3.7					
Kenya; 2011 – 2011	2.8	5.1					
Mali; 2012 –2014	11	15.9					
Morocco; 2010 2011	3.8	3.7					
Mozambique; 2011–2014	0	2.8					
Philippines; 2008–2015	7.6	5.9					

* Studies were eligible for the analysis if they tested >=90% of cases and reported at least five ALRI deaths (to ensure the precision of estimates).

† Detailed formulas in Chapter 3.

‡ Firstly, type–specific AFs for hPIV–ALRI cases were calculated using the median of type–specific odds ratios from two recent multi-country studies. The estimated AFs for each hPIV type and the prevalence of four hPIV types were input to yield the average AF for hPIV–ALRI cases (73%).

Table 6-7. Estimation of the global hPIV–attributable ALRI cases and deaths for children under five years

Outcome	Attributable fraction (AF, %)	Global hPIV–associated burden estimates	Global hPIV–attributable burden estimates*
hPIV–ALRI cases (million)	73%	29.5 (UR 19.2–46.7)	21.5 (UR 14.0–34.1)
hPIV–ALRI hospitalisations (*1,000)	73%	1,007 (UR 601–1,750)	735 (UR 439–1,277)
hPIV–ALRI deaths	66%	53,000 (UR 25,300–113,500)	35,000 (UR 16,700–74,900)

* Applying the corresponding attributable fraction to the estimates of hPIV–associated burden.

6.3. Conclusion and discussion

6.3.1. Implications

The estimates suggest that hPIVs are associated with about 21% of ALRI cases, 6–20% of ALRI hospitalisations, and 7% of ALRI mortality, indicating the importance of developing effective targeted prevention and treatment among children under five years. Infants are disproportionately affected by hPIV–ALRI morbidity and mortality burden, reflecting their immature immunity and the decay of maternal antibodies (Simon et al. 2015, Sangli et al. 2001).

The reduction in hCFRs with age was less marked than the reduction in hospitalisation rates with age. Children aged 12–59 months in low– and lower middle–income countries had a relatively high hCFR. This might reflect the virulence of hPIV and would have implications for prevention and treatment strategies – strategies only targeting infants are likely to be insufficient. Similar to IFV and hMPV, children hospitalised with hPIV–ALRI in low– and lower middle–income countries had the highest hCFRs, warranting continued efforts to improve the outcome of hPIV–ALRI in low– and lower middle–income countries.

6.3.2. Meta–analysis results by different stratification groups

The global estimates for hPIV–ALRI hospitalisations and in–hospital deaths were similar in different stratification groups (Appendix A10). The range of hospitalisations (447,000–1,427,000; Appendix A11) derived from the proportion–based approach was also broadly similar with the estimates using the incidence–based approach.

6.3.3. Long–term trend in hPIV burden estimates and variation between years

There were five studies with annual hospitalisation rates of hPIV–ALRI over five years or more for 0–59 months (Appendix A17). As shown in Figure A17–3 (Appendix A17), hospitalisation rates varied across years in each study. The maximum seasonal variation was mostly 3–5–fold, and in one study the seasonal variation could be as large as 12–fold. As aforementioned, the

uncertainties in the hPIV–associated burden estimates could have been underestimated due to the aggregation of yearly data.

No consistent secular trends were observed in the hospitalisation rates across the five studies: rates changed by 20% or less in three studies in Argentina and South Africa; rates increased substantially in the study in Thailand (0.4 per 1,000 children per year pre–2010 vs 1.1 after 2010) while decreased in the study in Kenya (2.0 per 1,000 children per year pre–2010 vs 0.9 since 2010).

6.3.4. Non–detection of hPIV–4 and adjustment for missing hPIV–4

The estimation of hPIV–associated ALRI burden was complicated by the co–existence of three–type (hPIV–1 to 3) and four–type data (hPIV–1 to 4). The ALRI burden associated with four hPIV types were modelled on two key parameters. One parameter was the prevalence of hPIV–4, which was estimated in a pooled analysis of hospital–based studies (Appendix A13). This prevalence was extrapolated to community–based studies. By doing this, the number of hPIV–ALRI cases might have been underestimated because hPIV–4 accounted for about 20% of all hPIVs during 2012–2017 in one community–based study detecting four hPIV types. The prevalence in total hospitalised ALRI was extrapolated to hospitalised ALRI with hypoxemia. It was impossible to assess how the extrapolation affected burden estimates because the information of serotype was unavailable in hypoxemic cases. The second parameter – hCFRs for four hPIV types – were estimated using very limited data (five studies) from high child mortality countries (Appendix A13). The type–specific hCFRs had wide and overlapping confidence intervals, especially for hPIV–2 and hPIV–4, reflecting the substantial variation across five studies and the limited precision. Additional relevant hPIV type–specific hCFR data are needed to refine the estimate.

6.3.5. Limitations related to diagnostic tests

PCR was used in 69% of hospitalisation studies in the main analysis for detection for hPIV. The remaining 31% studies used indirect immunofluorescence assay (IFA), culture, and a mix of PCR and other tests (culture and serologic test). IFA or culture shows lower sensitivity (about 50%) and similar specificity compared to molecular tests (Kuypers et al. 2006, Druce et al. 2005). Therefore, hospitalisation rates of hPIV–ALRI could have been underestimated due to the use of these tests.

6.3.6. Under–detection of hPIV and adjustment for the levels of testing

Similar to IFV and hMPV, incidence rates and hospitalisation rates of hPIV were adjusted for the levels of testing based on the assumption that the percent positivity for hPIV was the same in those tested and untested. hPIV–ALRI hospitalisation rates could have been biased in 23% of studies in which less than 90% of cases were tested due to refusal or cases being transferred or discharged (8%), cases being systematically sampled (8%), and unknown reasons (8%). In the remaining 77% of hospitalisation rate studies, at least 90% of cases were tested for hPIV. The under–detection might also cause an underestimation to the estimates of hCFR and in-hospital mortality as very severe cases and deaths are usually less likely to be tested (Feikin et al. 2017). Consistent with this, data from the current systematic review showed that hCFR in those tested was higher compared to those untested (Appendix A7).

6.3.7. Limitations for hPIV–ALRI overall mortality

The estimate of overall hPIV–associated ALRI mortality was modelled using two approaches (“inflation factor” and “the proportion positives of hPIV–ALRI deaths”). The analyses were susceptible to the limitations similar to the analysis for hMPV, which are explicated in Chapter 4 and 5. The assumptions and limitations will be discussed in detail in Chapter 7. The estimates for high child mortality settings were broadly similar in the two approaches.

6.3.8. hPIV–attributable burden estimates

The hPIV attributable burden estimates suggest that hPIV can cause about 16% of ALRI cases, 4–14% ALRI hospitalisations, and 4% of ALRI mortality in children under five years (McAllister et al. 2019, WHO 2018, Troeger et al. 2018). The assumption for the analysis of hPIV–attributable ALRI deaths is similar to the analysis for IFV and hMPV. The assumption will be discussed in detail in Chapter 7. The point estimate of hPIV–attributable mortality in high child mortality countries increased by 30% in another approach using the proportion of hPIV-attributable ALRI deaths based on data from CHAMPS (Appendix A16).

Chapter 7 Overall findings, strengths and limitations

7.1. Overall findings

Table 7–1 shows an overview of the estimated faction of influenza virus, human metapneumovirus and human parainfluenza virus in child ALRI cases, hospitalisations, and deaths in this thesis. In general, hPIV appears to account for a higher proportion of ALRI morbidity and mortality in children under five years, followed by IFV and hMPV. Compared with IFV, hMPV accounts for a lower proportion of ALRI hospitalisations and deaths, while a higher proportion of ALRI cases. Estimation of hMPV and hPIV burden are preliminary based on fewer datapoints than IFV, so can be refined when data are more available in future. For example, future additional studies are needed to assess and verify whether the higher proportion of hMPV in ALRI cases indicates the “true” larger impact of hMPV in non–severe ALRI cases than IFV in young children or it is due to an overestimation to the number of hMPV–ALRI cases. Overall, the burden estimates of the three viruses are likely to be conservative because some cases might have been missed as many factors can influence test results and cause a false negative diagnosis. Vaccine probe studies can help better understand the true impact of hMPV and hPIV with the availability of effective vaccines against the two viruses. Additionally, the true number of cases requiring hospitalisation is likely to be higher than the estimates, especially in regions with limited healthcare capacity and poor access to care.

On the other hand, as presented in Chapter 1, the carriage of respiratory viruses in upper respiratory tract of healthy children and children with mild infections is common, and the detection of a virus does not necessarily suggest causal association between the detected virus and ALRI. Thus, this thesis incorporates the attributable fractions for the three viruses into analyses and makes attempts to quantify the true role of the three viruses in causing ALRI morbidity and mortality.

According to a recent multi–country analysis, viruses cause about two times as many ALRI hospitalisations as bacteria among children under five years in low–income and low middle–income settings with widespread uptake of *Haemophilus influenzae type b* (Hib) vaccine and pneumococcal conjugate vaccine (PCV)(Pneumonia Etiology Research for Child Health Study Group (PERCH) 2019). Respiratory syncytial virus, IFV, hMPV, and hPIV are found to be the leading causative viral pathogens of childhood ALRI, accounting for a large fraction of the cases. The substantial burden associated with hMPV and hPIV in the present work highlights the potential benefit of targeted vaccines and treatment in reducing ALRI morbidity and mortality due to the two viruses, especially hPIV, in young children. The availability of such interventions and increased uptake of influenza immunisation for young children and pregnant women will facilitate and accelerate the progress towards meeting the Sustainable Development Goal 3 of reducing one–third of under–five mortality between 2017 and 2030 (United Nations 2019).

For all three viruses, age stratified estimates highlight the importance of developing targeted interventions for infants, including maternal immunisation, active immunisation, and antiviral drugs. High hCFR estimates in low– and lower middle–income countries warrant continued efforts and investment to reduce ALRI mortality by improving child health condition (e.g., nutrition), immunisation, access to care, testing capacity and practice, and the quality of care in these countries.

Table 7-1. The faction of influenza virus, human metapneumovirus and human parainfluenza virus in ALRI cases, hospitalisations and deaths among children aged 0–59 months.

	ALRI cases	ALRI hospitalisations	ALRI deaths
Virus associated ALRI*			
IFV	7%	5-17%	3%
hMPV	11%	4-13%	2%
hPIV	21%	6-20%	7%
Virus attributable ALRI			
IFV	5%	4-13%	2%
hMPV	8%	3-10%	1%
hPIV	16%	4-14%	4%

* The proportion of ALRI cases, hospitalisations and deaths that are detected positive for the three viruses.

7.2. Strengths

As summarised in Chapter 1, one of the major strengths of this work is the incorporation of unpublished data on the incidence, hospitalisations, hCFRs of virus–specific ALRI from different geographic locations, especially from low– and lower middle–income countries. The incidence rate–based approach requires fewer assumptions compared to proportion–based approach. The inflation factor approach is straightforward. The assumptions related to the inflation factor approach mostly arise from the input data. Assumptions and limitations that have been presented in Chapter 4–6 will be discussed in this chapter. Additional assumptions and limitations will also be discussed in detail.

The detailed datasets shared from the collaboration network also allow for the estimation of several parameters that are difficult to obtain from published literature. These estimates include (1) “the proportion of virus–associated ALRI deaths”, (2) “the hCFR for each hPIV type” (mainly estimated using data from PERCH), and (3) “the attributable fraction (AF) for virus–associated deaths”. The first estimate leads to the development of an alternative approach (in sensitivity analysis) for overall mortality of virus–specific ALRI. A mixture of different approaches was used to triangulate the mortality estimates. The hPIV type–specific CFRs allow for the adjustment for missing hPIV–4 in three type hCFR studies, helping refine the estimation of mortality associated with four hPIV types. While the mere presence of respiratory viruses in a child dying from ALRI may not indicate causal association, the AF estimates assist in reporting virus–attributable mortality, in order to derive estimates which may be closer to the true role in ALRI mortality than the virus–associated mortality.

7.3. Limitations

To summarise, the uncertainty ranges of estimates of the three viruses are all very wide, reflecting the paucity of data and differences between studies, including differences in viral epidemiology between populations and differences

in methodology. This thesis presents the first estimates of global burden of hMPV– and hPIV–ALRI among young children. In light of the paucity of data at regional levels for hMPV and hPIV, the estimates for hMPV and hPIV should be viewed as preliminary estimates. Additional studies reporting burden estimates are needed to improve the estimates for the two viruses. Next section is focused on specific limitations.

7.3.1. Heterogeneity between studies

A high level of between–study heterogeneity was observed in forest plots, indicating the substantial differences in estimates from different studies. Heterogeneity is usually broadly classified as epidemiological differences and methodological differences. One recommended approach is to incorporate the epidemiological heterogeneity into a meta–analysis model (e.g., classical random effect model and generalised linear mixed model) (Schroll et al. 2011). Such model assumes that the effects from different studies are not identical but follow some distribution (normal distribution are commonly used). As a result, the combined estimate from such model can only be interpreted as the average effect across all studies rather than the “true” effect estimated in a fixed effect model as “true” effects can vary (Higgins JPT 2011, Riley et al. 2011). Methodological heterogeneity is dealt with in the same way as epidemiological heterogeneity because it is challenging to distinguish them. However, the presence of methodological differences usually lead to overestimation or underestimation in the combined estimate.

Heterogeneity in methodology was systematically assessed in all studies and was found for each outcome, which would indicate the presence of biases and affect the estimates in included studies. Certain biases could be dealt with statistically. For example, the testing practice was different between studies; incidence and hospitalisation rates were adjusted for different levels of testing to account for the extents of under–detection. This adjustment, however, could

have biased estimates in certain studies as discussed in the chapter 4–6. To summarise, when adjusting for the under–detection of viruses, it was assumed that the percent positivity for a given virus (any of IFV, hMPV, and hPIV) was the same in those tested and untested. The reasons for not testing were unavailable in a few studies, and it is suspected that rates in these studies are likely to be biased after the adjustment. Even in studies with relevant information, certain reason for not testing (i.e., not testing because of refusal) provided little information on how the adjustment could affect rates. Moreover, it was impossible to adjust for under–detection in studies where the level of testing was unavailable, and in these studies rates could have been underestimated. Available data from hospital–based studies show that children who were not tested for the three viruses tended to have a higher case–fatality ratio than those who were tested. The findings are consistent with the observation and understanding that patients with severe infections and fatal cases are usually under–detected (Feikin et al. 2017). This suggests that the estimates of hCFRs and mortality of virus–ALRI might have been underestimated. One recent multi–country analysis showed that the detection of hPIV was negatively associated with disease severity in children under five years; the differences for IFV and hMPV were less obvious (Pneumonia Etiology Research for Child Health Study Group (PERCH) 2019). Thus, a higher level of severity among untested patients might indicate an overestimation to hPIV hospitalisation rates after adjusting for the under–detection of hPIV.

For other biases arising from methods, the magnitude is difficult to quantify because different estimates between studies could reflect both the methodological heterogeneity between studies and the inherent difference in a given virus' epidemiology between populations. Meta–regression analysis has been used to identify characteristics affecting the estimates of interest and to quantify their impact. This, however, is inappropriate in the present work because the "real" difference between populations and seasons could confound

and blur the true association between methodological characteristics and estimates. Several key methodological factors can affect burden estimates, but their influences were not dealt with statistically in this thesis. One of the key factors is the test method. Heterogeneity mainly came from differences in the sensitivities and specificities of various test methods. Since the sensitivity of a given test may vary by viruses, the potential bias regarding this issue has been discussed separately for each virus (in Chapter 4–6). To summarise, traditional test methods usually have lower sensitivities and similar specificities compared to molecular tests, producing false negative test results more commonly than false positive test results. Thus, numbers of virus–positive cases and infection rates could have been underestimated in studies using these test methods. Other factors are summarised below.

Case ascertainment

There are two types of case ascertainment: active ascertainment (active studies) and passive ascertainment (passive studies). In active studies, cases were identified actively through regular household visits, while in passive studies, cases were only identified when patients sought care in healthcare facilities. By viruses, 9–21% community–based studies were conducted in clinics, offices of general practice, and outpatient departments in high–income countries. Other community–based studies are active household studies. The identification of cases in active studies does not rely on care–seeking, so active studies are likely to provide estimates closer to the “true” virus–ALRI burden in a defined catchment area. However, active studies are extremely rare because the establishment and follow–up is resource–intensive.

All the hospital–based studies included in the analysis are passive studies. Passive studies are efficient in identifying severe viral respiratory infections requiring hospital care. However, in addition to the perceived severity of illnesses, whether a patient presents to or is admitted to hospitals is often related to geographic accessibility, healthcare cost, and healthcare services. In

addition to hospitals, patients may go to traditional healers, drug sellers, or choose not to seek any care (Webair and Bin-Gouth 2013). Therefore, the potential number of severe cases requiring hospitalisation is likely to be higher than the current estimate in resource–limited regions. Care–seeking can vary substantially within and between countries, which makes it difficult to quantify the underestimation in the estimate of global hospitalisations (Deutscher et al. 2012, Jordan et al. 2009, Breiman et al. 2011, Wong et al. 2018). Pneumonia care–seeking data in UNICEF show that an average of 62% of children with pneumonia symptoms did not seek formal health care in 86 high child mortality regions or countries, indicating the estimates of hospitalisations could have been considerably underestimated in high child mortality countries (UNICEF 2016).

Population denominator

In addition to case ascertainment, infection rates can also be affected by the denominator. Ideally, individually recorded person–time at risk should be the most accurate denominator for estimating infection rates. However, more than 80% of hospital–based studies used official population estimates (e.g., the mid–year population for a given catchment area). Using official population estimates has an advantage of saving efforts and resources. The disadvantage is that the official population estimates are not necessarily available for the defined catchment area served by the study hospitals. Sometimes the official estimates may be only available for a broader or a smaller area than the study hospitals provide care for. Hospital–based studies in the main analysis could be classified into: (1) the official population estimates were available for the exact catchment area (or similar area) that the study hospitals served; (2) the original official population estimates were available for a broader area, but were adjusted to deduct the non–catchment population, who were not served by the study hospitals. The adjustment can improve estimates of hospitalisation rates by avoiding the overestimation of denominators. However, relevant information is

lacking in nine studies with data on IFV hospitalisation rates, and it is uncertain whether the denominator was overestimated or not.

Study design

In ALRI aetiology studies, specimens are usually collected when children present to or are admitted to health facilities. Therefore, included studies are all cross–sectional in terms of the sequence of exposure (viral infections) and outcome (ALRI). Nevertheless, included studies could still be divided into two types according to whether the cases were identified prospectively (according a pre–specified method) or retrospectively. By viruses and outcomes, 0–25% of studies were retrospective (Appendix A18). These studies mostly identified cases using retrospective records, such as hospital discharge records, and provided little information on the case enrolment or sampling. It is suspected that estimates from these retrospective studies are more likely to be biased than prospective studies.

Patient groups excluded

By outcomes, 0–14% of studies in the main analysis excluded children with certain high–risk conditions. These conditions include heart disease, chronic lung disease, metabolic and genetic diseases, immunosuppression, and prematurity. As summarised in Chapter 1, excluding patients with underlying conditions might lead to an underestimation to the rates of virus–ALRI and the risk of mortality due to these infections.

By outcomes, 10–33% of studies in the main analysis excluded neonatal data (neonatal hospitalisation rates or hCFRs). To assess the impact, hospitalisations of hMPV–ALRI for 0–5 months were estimated by summing up the estimates for neonates and for 1–5 months; the estimate was comparable to the estimate for 0–5 months as an overall group. In studies reporting neonatal hCFRs, most studies had a very small number of all–cause ALRI deaths (less than five

deaths) for neonates. A subgroup analysis for neonates was not performed due to the limited precision and the small number of studies. The estimates of mortality might be biased due to the exclusion of neonates in several hCFR studies.

Case definition

For most outcomes, less than 30% of studies used case definitions different from the standardised case definition (Appendix A18). The proportion is higher (about 40–50%) for IFV–ALRI hospitalisation rate and the proportion of hMPV and hPIV in hospitalised ALRI cases. The non-standardised case definitions used in hospital–based studies were generally similar for the three viruses. These definitions include hospitalised ARI, hospitalised ARI or fever, hospitalised ARI with fever, hospitalised ALRI or croup (for hPIV), and hospitalised with respiratory and non-respiratory diseases associated with IFV (limited to IFV). Using definitions that are broader than the standardised case definition, such as hospitalised ARI, hospitalised ARI or fever, and hospitalised ALRI or croup (for hPIV) can capture not only the hospitalised virus–ALRI cases, but also hospitalised virus–acute upper respiratory infections (AURI). Therefore, using these broader definitions could have caused an overestimation to the hospitalisations of virus–ALRI. Using “hospitalised ARI with fever” is likely to identify a broader group of cases than “hospitalised ALRI” as fever is reported to lower the sensitivity of ALRI only marginally, while ARI increases the sensitivity (Cardoso et al. 2011). Even in studies using the standardised case definition, heterogeneity could also exist because the physician’s judgement could vary between facilities.

Most of the hCFR studies (85–93%, varying by the three viruses) in the main analysis used the standardised case definition. Other studies used “hospitalised ARI” and “hospitalised due to respiratory and non-respiratory diseases associated with IFV”. However, it is uncertain how these definitions affected the

hCFR estimates. The cases, though not defined as ALRI, were severe enough to require hospital admission, which might indicate similar disease severity.

7.3.2. Precision of estimates

hCFR studies had relatively small sample sizes (i.e., small numbers of virus–confirmed ALRI cases), so hCFR estimates were less precise compared with other measures. The median study size was 52 (IQR 31–120) for IFV, 45 (IQR 14–109) for hMPV, and 55 (IQR 28–109) for hPIV. The precision of individual studies decreased as data were further stratified by age groups. Small studies were not excluded for two reasons. First, excluding small studies could lead to the loss of information. Second, the precision of estimates in individual studies were incorporated into the combined estimates in the meta–analysis. A meta–analysis yields a weighted average by combining individual studies, and smaller studies tend to have smaller weights.

Yearly data on incidence rates, hospitalisation rates, and hCFRs were aggregated to ensure the precision of estimates in the age– and region–stratified analysis. However, the variation in these estimates between seasons were not accounted for (Appendix A17). Therefore, the true uncertainty of burden estimates is likely to be broader.

7.3.3. Lack of viral respiratory infection burden data

Incidence, hospitalisations and in–hospital deaths

The generalisation of meta–estimates is limited because data on virus–ALRI incidence, hospitalisations and hCFRs were only available for limited sites and time points. For example, for hMPV and hPIV, there were very few data from Eastern Mediterranean and European region. This also leads to one of the limitations that this work is unable to develop country–specific burden estimates, which is relevant to national policy. However, this work intends to estimate the overall impact of the three viruses, especially hMPV and hPIV, for which global

burden estimates in young children have not been made, informing future new public health research and surveillances on the viruses. The availability of local research and surveillances in future will facilitate the estimation of country–specific burden.

7.3.4. Data from all time points (from 1990's to 2010's) were aggregated together in the present meta–analysis. A key assumption is that the global burden of virus–ALRI did not change over time. Multi–year data suggest that the trend in hospitalisation rates of virus–ALRI can be different between sites. The rate can remain unchanged at some sites, while increase or decrease at other sites (Appendix A17). These multi–year studies, however, constitute only a small fraction of included studies. In another sensitivity analysis, the estimate of IFV-associated hospitalisations remained similar after excluding data prior to 2010 (Appendix A8). For hMPV and hPIV, fewer data were available compared to IFV, which did not allow for such analysis. It was more challenging to assess how incidence rates and hCFRs changed over time due to the scarcity of multi–year incidence rates and the small number of virus–ALRI deaths.The estimation of overall virus–ALRI deaths

Current results suggest that over 50% of ALRI deaths occur in the community, for which specific viral diagnosis is usually unavailable. Different analytical models were used to estimate the virus–specific ALRI mortality, and potential biases and limitations for each model are summarised in Chapter 4 and 5. In addition to those specific biases, several limitations that are common to all models should be noted. First, data were limited in all the models, and additional data from diverse geographical regions could improve the mortality estimates. Second, the overall mortality of virus–ALRI was estimated using multiple approaches in this thesis. Due to the scarcity of virology testing in the community setting, especially for ALRI deaths, it was difficult to obtain the "ideal" data for each model. Several types of data were used as proxies of the "ideal"

data, varying by different settings and different viruses. Table 7–2 shows a summary of input data and assumptions in the main analysis. However, no evidence validating the assumption regarding using these data as proxies were identified. Violations of this assumption could bias the estimates of virus–ALRI overall mortality. Post–mortem studies may provide information that helps test the assumptions and improves the understanding of the causes of child ALRI deaths (Turner et al. 2012, CHAMPS). However, it should be noted that post–mortem studies are susceptible to several biases caused by the low acceptability, microbiological contamination and pathogen degradation (Turner et al. 2012).

Table 7-2. A brief summary of input data and assumptions for virus–ALRI overall mortality (inflation factor) estimation in the main analysis.

		IFV	hMPV	hPIV
high child mortality settings	Input data	The number of pneumonia deaths by locations (inpatient versus outpatient and emergency departments, clinics, on the way to healthcare facilities, and at home)		
	Main assumption and limitations	The percent positivity of a given virus in total ALRI deaths in hospital settings was the same with that in community settings. Or in other words, the location of the ALRI deaths would be agnostic of the pathogen. The estimated inflation factor was generalizable to other regions and countries with high child mortality.		
low child mortality settings	Input data	The number of IFV–associated deaths among children aged 0–17 years in the US	The proportion of children aged 0–59 months with pneumonia symptoms seeking care	
	Main assumption and limitations	The inflation factor estimated using the US data might not be generalizable to other countries with low child mortality. The inflation factor for 0–17 years might be different from that for 0–59 months.	The inflation factor is likely to be underestimated using such data because the definition of "care–seeking" in the input data is broader than the definition of "in–hospital". The case–fatality ratio (CFR) among children with pneumonia who did not seek care could be different from the CFR in children seeking care, so the care–seeking in children with pneumonia symptoms could be different from children who died from pneumonia.	

7.3.5. The estimation of virus–attributable ALRI mortality

In this thesis, attempts were made to estimate the virus–specific attributable ALRI mortality using two approaches – “the attributable fraction (AF) for virus–associated ALRI deaths” and “the percent of virus–specific attributable ALRI deaths”. For the first approach, the AF for virus–specific associated ALRI deaths, which are not readily available in published reports, was modelled by assuming that the hCFR for virus–unattributable cases was equal to the hCFR for virus–negative cases. A wide range of pathogens, including viruses and bacteria, which co–exist with IFV, hMPV and hPIV, are possible causes of the unattributable ALRI (Panda et al. 2014, Zhong et al. 2019, Nolan et al. 2017). Therefore, virus–negative cases, caused by a mix of pathogens (including viruses and bacteria) except for the virus of interest, were used to resemble the spectrum of causative pathogens of unattributable cases. The lower hCFRs for virus–attributable cases compared with virus–unattributable cases, as derived from the model, is generally consistent with the understanding that bacterial–viral co–infections are associated with increased severity (Ruuskanen et al. 2011, Brealey et al. 2015). However, no direct evidence was found to validate this assumption. Violations of this assumption could bias the estimates of virus–attributable ALRI mortality.

The second approach was developed with CHAMPS data. The cause of ALRI deaths is ascertained based on the test result of post-mortem specimens and other individual information, including laboratory, histopathology and verbal autopsy, following a standardised procedure (CHAMPS , Blau et al. 2019). Although CHAMPS provides valuable data that improves the understanding of causes of ALRI deaths, several potential limitations should be noted as discussed in a recently published paper (Salzberg et al. 2019). First, some deaths at the sites may be missed. The findings among captured deaths might differ from missed deaths. Second, CHAMPS network includes seven sites in Sub–Saharan Africa and South Asia, the estimated viral attribution of these sites

might not be generalizable to other regions and countries with high child mortality (e.g., the region of Americas). Third, although CHAMPS has conducted community–based and facility–based surveillance, the majority of the enrolled deaths during the initial phase of the surveillance were identified through health facilities. Fourth, CHAMPS provide site–combined data. Differences between sites could not be accounted for when analysing the combined dataset, thus the uncertainty of virus–attributable mortality estimates could have been underestimated.

7.3.6. Potential limitations in data from UN and WHO

The burden estimates in this work were dependent on the estimates from UN Inter-Agency Group on Mortality Estimation on the under–five mortality rates in several ways. First, the burden estimates were calculated using UN Population estimates, which were estimated using the UN mortality rate estimates. Second, meta–analyses were stratified into two groups based on the UN mortality rate estimates. Third, in the sensitivity analysis, the overall hMPV– and hPIV–ALRI mortality estimates for high child mortality settings were developed using WHO child ALRI mortality estimates. Since the WHO child ALRI mortality estimates were modelled on the UN mortality rate estimates and data on cause-of-death, the hMPV– and hPIV–ALRI mortality estimates for high child mortality settings (in sensitivity analyses) were also partially dependent on the validity of UN mortality rate estimates.

The UN population and mortality estimates were chosen in current analyses to promote global consistency and to allow for comparison between the updated IFV burden estimates and the previous estimates (McAllister et al. 2019). However, a recently published study compared 2017 UN child mortality rate estimates with IHME estimates and found a relative difference greater than 10% in the under–five mortality rate estimates in 32 countries (Hug et al. 2019). The largest differences were found in certain African countries and Asian countries

with different input data and countries with conflicts or civil unrest and high HIV prevalence (Alkema and You 2012). The uncertainty of under–five mortality rate estimates in these countries could have affected our global and regional burden estimates of IFV, hMPV and hPIV.

Chapter 8 In sensitivity analyses, WHO under–five ALRI mortality estimates for high child mortality settings were used to derive the hMPV– and hPIV–ALRI mortality estimates for this setting. There has been a debase about the differences between WHO under–five ALRI mortality estimates and the estimates modelled by IHME. The 2017 WHO estimates are generally similar to IHME estimates in African region and region of Americas (less than 10% of difference), and slightly different in Eastern Mediterranean region (27%) and South-East Asia region (20%), with the largest difference observed in European region (about 50%) (WHO 2018, Institute for Health Metrics and Evaluation (IHME) 2020). Thus, for high–child mortality settings which do not include the European countries, the WHO ALRI mortality estimates were generally consistent with the IHME estimates. However, there are still uncertainties in WHO ALRI mortality estimates associated with model uncertainty and quality of data on cause-of-death, especially in countries without adequate vital registration systems (Li Liu et al. 2015). These uncertainties could have affected the hMPV– and hPIV– ALRI mortality estimates for high child mortality settings.

Proposals for improving future burden estimates and implications for immunisation

8.1. Proposals for improving future burden estimates

The discussion in the foregoing paragraphs and chapters have revealed the gaps that existed in data and analysis. One general issue is that data on virus–associated ALRI incidence, hospitalisations, and mortality are not available for most parts of the world, and where the data are available, data are only available for certain years or seasons. Studies initiated in regions with no /

In sensitivity analyses, WHO under–five ALRI mortality estimates for high child mortality settings were used to derive the hMPV– and hPIV–ALRI mortality estimates for this setting. There has been a debase about the differences between WHO under–five ALRI m

limited data should be encouraged because they can provide valuable information for local policy makers and help refine the global burden estimates. Countries, especially those with high child mortality, can expand existing influenza sentinel surveillances or undertake new sentinel surveillances to quantify the local public health impact of hMPV and hPIV (e.g., hospitalisations), which in turn would help refine the global burden estimates.

Of all outcomes, incidence rates in the community is one of the scarcest type of data. In high–income countries with good care seeking, records from outpatient and general practitioner offices offers an opportunity to estimate the virus–associated incidence. Efforts should be made to increase the availability of data by publishing them in papers or on webpages. For example, linking clinical care patient level data to virology dataset allows for the estimation of virus–associated burden in community and hospital settings in some regions (Simpson et al. 2015). In other regions with poor care seeking, the incidence can be only estimated in community–based studies with household level follow-up, which requires considerable funding and resources to initiate and to maintain.

With the availability of maternal and paediatric influenza vaccines, vaccine probe studies provide an alternative option for quantifying the contribution of influenza in causing ALRI among young children. Since vaccine probe studies do not require viral diagnosis, they have the advantage of accounting for infections that are undetectable at specimen collection and accounting for influenza virus' contribution in predisposing children to substantial bacterial infections. Despite of the advantages, results from vaccine probe studies can be affected by the efficacy of influenza vaccines that are used, which can vary by seasons. Trials using maternal influenza vaccine as the probe have estimated the proportion of ALRI hospitalisations attributable to influenza among infants under 6 months (Omer et al. 2018).

In sensitivity analyses, WHO under–five ALRI mortality estimates for high child mortality settings were used to derive the hMPV– and hPIV–ALRI mortality estimates for this setting. There has been a debase about the differences between WHO under–five ALRI m

Global Influenza Surveillance and Response System (GISRS) provides data on influenza activity across many countries, which have been used to estimate influenza associated disease burden at the global level (World health Organization 2020, Simonsen et al. 2013, Iuliano et al. 2018). The system can be expanded to include the detection of hMPV and hPIV providing detailed virology data, which may be used to estimate hMPV and hPIV disease burden and inform potential upcoming immunisation strategies.

The virus–associated ALRI overall mortality estimates were modelled on in–hospital deaths. The estimation of in–hospital mortality can be improved by incorporating post–mortem tests to improve the viral diagnosis in children who die before specimen collection. Moreover, since post–discharge mortality accounts for a substantial fraction of mortality, especially in high child mortality countries, hospital–based studies are encouraged to follow up children who are discharged from hospitals (for several weeks) to identify children who deteriorate or die following discharge (Pneumonia Etiology Research for Child Health Study Group (PERCH) 2019, Wiens et al. 2013). The establishment of high–quality regional and national health information systems can capture and record virus–confirmed cases and deaths, which can improve the quality and precision of the mortality estimates.

For the estimation of overall virus–ALRI deaths, estimates can be refined by increasing the availability of several types of data with the presence of multiple models.

- The number of ALRI deaths occurring in hospital settings (i.e., deaths in inpatient departments) and the number of ALRI deaths occurring in community settings (i.e., deaths at home, on the way to health facilities, in outpatient departments and emergency departments) within a defined catchment area. In some regions, especially high–income countries, relevant data may have been collected, while not readily available in

In sensitivity analyses, WHO under–five ALRI mortality estimates for high child mortality settings were used to derive the hMPV– and hPIV–ALRI mortality estimates for this setting. There has been a debase about the differences between WHO under–five ALRI m

public reports. For example, relevant data were identified in vital statistics in the US (Centers for Disease Control and Prevention and National Center for Health Statistics). The collection of relevant high–quality data in resource–limited regions is dependent on the development of death registration systems like Health and Demographic Surveillance System (HDSS) and INDEPTH Network and the use of tools (e.g., verbal autopsy) for establishing the cause of death (Ye et al. 2012). In addition, the estimation of future estimates requires new data because care seeking may change over time. For IFV, the generalisation of inflation factor in low child mortality settings can be improved when location–specific IFV–associated ALRI deaths are readily available in more regions.

- The proportion of virus–associated ALRI deaths in total ALRI deaths among children under five years. Relevant data should be more available in healthcare facilities than in the community because of the availability of virology tests. The collection of community mortality data and a full understanding of the aetiology of child ALRI deaths in both healthcare facilities and communities rely on the establishment of post–mortem surveillances like the CHAMPS Network. Regression models have also been used to estimate the impact of certain viruses. Compared to regression models, using observational data (i.e., the proportion of virus–associated ALRI deaths) does not require advanced model techniques and regression related assumptions. However, observational data are likely to underestimate the impact of a virus because the virus may be undetectable at specimen collection. Moreover, it is challenging to quantify the burden of cardiovascular or all–cause mortality associated with a virus (e.g., IFV) using observational data because children with non–respiratory infections are less likely to be tested.

- Similar to IFV, it may be possible to estimate the burden associated with hMPV and hPIV in regression models using the weekly or monthly

In sensitivity analyses, WHO under–five ALRI mortality estimates for high child mortality settings were used to derive the hMPV– and hPIV–ALRI mortality estimates for this setting. There has been a debase about the differences between WHO under–five ALRI m

number of deaths and the concurrent virus activity data within a defined catchment area. But in the present work, it is impossible to develop such models due to the unavailability of data. Relevant data can be collected within existing influenza surveillance systems in future to develop regression models.

In addition to the above, for IFV, the adjustment of influenza vaccination in future estimates requires vaccine coverage data among young children and pregnant women and the vaccine effectiveness by seasons. The adjustment will become increasingly necessary as maternal and paediatric influenza vaccine strategy is likely to be adopted in more countries in future. Studies assessing the global distribution of influenza vaccine doses found that despite the overall increase in the number of distributed doses between 2004 and 2011, the distribution of influenza vaccine was highly uneven in and across WHO regions with 95% of doses being distributed to three WHO regions – the region of Americas, European region and Western Pacific region, and only 5% of doses being distributed to 50% of the world's population (Palache et al. 2017). WHO and UNICEF have been monitoring and evaluating national influenza immunisation policies and uptake in WHO member states (Ortiz et al. 2016). However, available global reports only focused on the national influenza coverage in general population, with no information regarding influenza uptake for specific subgroup population (e.g., in young children and pregnant women). Influenza coverage for children and pregnant women have not been readily available in most parts of the world, except in some European countries and in the region of Americas (Palache et al. 2014, Pan American Health Organization 2015, European Centre for Disease Prevention and Control 2017). By reporting influenza vaccine coverage in subgroup population, WHO and UNICEF can improve influenza vaccination monitoring, especially in high–risk groups, and facilitate improvement on global and national influenza burden estimation in

In sensitivity analyses, WHO under–five ALRI mortality estimates for high child mortality settings were used to derive the hMPV– and hPIV–ALRI mortality estimates for this setting. There has been a debase about the differences between WHO under–five ALRI m

future. To improve the global hPIV burden estimates, hPIV–4 should be tested more often as is being done for hPIV–1 to hPIV–3.

8.2. Implications for immunisation

Vaccination is the most effective way to prevent influenza infections and severe outcomes related to the infections. Although it is recommended that young children and pregnant women be prioritised for influenza immunisation, only a small fraction of low– and middle–income countries have adopted national maternal or paediatric influenza vaccination programs (M. C. Nunes and S. A. Madhi 2018). The substantial IFV–associated burden estimates in low– and lower middle–income countries indicate the importance to adopt national maternal and paediatric influenza immunisation programmes in these countries. Moreover, evidence suggests that vaccinating children can provide substantial benefits for non-vaccinated population through herd immunity effect, especially vulnerable population (e.g., older population) (Ropero-Alvarez et al. 2016). This strategy is of great significance in view of the limited effect of influenza vaccines for older people (Kim 2014). To achieve better and longer protection, many factors, such as the vaccination timing and the number of influenza vaccine doses administrated per year, should be considered in immunisation strategies (Young et al. 2018, Grohskopf et al. 2019).

Progress has been made in the development of hMPV and hPIV vaccines. As summarised in Chapter 1, several types of vaccines against hMPV and hPIVs are under investigation. One live–attenuated recombinant hMPV vaccine has recently been evaluated in a recent phase I clinical trial, and several hPIV–3 candidate vaccines have been evaluated or are under evaluation in phase I and II clinical trials (San Mateo et al. 2017, Karron et al. 2011, Bernstein et al. 2011, Bernstein et al. 2012). It has been shown that three–dose hPIV vaccines can substantially increase antibody levels of vaccine recipients (Bernstein et al. 2011). The vaccine development is currently focused on children older than 6 months and adults, while little is known about vaccines for young infants under 6

In sensitivity analyses, WHO under–five ALRI mortality estimates for high child mortality settings were used to derive the hMPV– and hPIV–ALRI mortality estimates for this setting. There has been a debase about the differences between WHO under–five ALRI m

months. Additional efforts and investment should be encouraged to accelerate the development of hMPV and hPIV vaccines in the future.

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Chapter 9 Conclusions

This thesis shows that IFV is associated with 7% of ALRI cases, 5–17% of ALRI hospitalisations, and 3% of ALRI deaths among children under five years. hMPV is associated with 11% of ALRI cases, 4–13% of ALRI hospitalisations, and 2% of ALRI deaths. hPIV is associated with 21% of ALRI cases, 6-20% of ALRI hospitalisations, and 7% of ALRI deaths. Future progress in reducing ALRI morbidity and mortality requires targeting prevention and treatment for young children, especially infants. Additional efforts are needed to improve the outcome of children in low– and lower middle–income countries who are infected with the three viruses.

Several challenges remain to be addressed to improve the estimation of global burden of virus–ALRI. First, the availability of data on virus–ALRI incidence, hospitalisations, and mortality is limited to a very small fraction of regions and discrete seasons. Existing influenza sentinel surveillances can be expanded to include the detection of other important respiratory viruses (e.g., RSV, hMPV and hPIV) to improve the availability of data on virus–ALRI burden, especially hospitalisations. Second, the identification of post–discharge mortality and the presence of good health service information systems with complete records of virus–confirmed deaths would substantially improve the mortality estimates. Third, the availability of simple and rapid viral diagnostic tests with good sensitivity and specificity would contribute to the identification of virus–associated infections and deaths in primary care facilities (Merckx et al. 2017). Post-mortem testing would assist in addressing the gaps existing in the cause of child ALRI death and improving virus–specific mortality estimates. Additionally, refinement of mortality estimates at national and global level is impossible without complete death registration systems and sample–based mortality surveillance systems (e.g., in China and India), and valid methods to establish the cause of death (e.g., medical certificate of cause of death and verbal

autopsy) (Shiwei Liu et al. 2016, Liu et al. 2019). These challenges need to be addressed to develop and improve national and global disease burden estimation.

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Chapter 10 Appendices

A1. Glossary

Abbreviation	Full name
AF	attributable fraction
AFR	African region
AMR	Region of the Americas
ALRI	acute lower respiratory infection
APAAP	alkaline phosphatase and monoclonal anti–alkaline phosphatase
ARI	acute respiratory infection
BAL	bronchoalveolar lavage
CI	confidence interval
CHAMPS	Child Health and Mortality Prevention Surveillance
d	day(s)
DFA	Direct fluorescent antibody test
DHS	Demographic and Health Survey
ELISA	enzyme-linked immunosorbent assay
EIA	EIA: enzyme immunoassay.
EMR	Eastern Mediterranean region
ETA	endotracheal aspirate
EUR	European region
HI	hemagglutination-inhibition assay
HICs	high income countries
hMPV	human metapneumovirus
hMPV–ALRI	human metapneumovirus–associated ALRI
hPIV	human parainfluenza virus
hPIV–ALRI	human parainfluenza virus–associated ALRI
ICU	Intensive care unit
IF	immunofluorescence
IFA	indirect immunofluorescence assay
IFV	influenza virus
IFV–ALRI	Influenza–associated ALRI
IHME	the Institute for Health Metrics and Evaluation

Abbreviation	Full name
ILI	influenza–like illness
INDEPTH	the International Network for the Demographic Evaluation of Populations and their Health
IVAC	International Vaccine Access Center
LICs	Low income countries
IMCI	Integrated Management of Childhood Illness
LMICs	Lower middle income countries
m	month(s)
MICS	Multiple Indicator Cluster Survey
MN	micro-neutralization assay
MV	mechanical ventilation
NA	Not applicable
NPA	nasopharyngeal aspirate
NPS	nasopharyngeal swab
NPW	nasopharyngeal wash
NS	nasal swab
NW	Nasal wash
OP	oropharyngeal
OPS	oropharyngeal swab
PAHO	Pan American Health Organization
PCR	polymerase chain reaction
PCV	pneumococcal conjugate vaccine
PERCH	Pneumonia Etiology Research for Child Health Study Group
PNE	Pneumonia
pSBI	Possible severe bacterial infections.
RIDT	Rapid influenza diagnostic test
RSV	respiratory syncytial virus
SARI	severe acute respiratory infection
sALRI	Severe acute lower respiratory infection
SEAR	South–East Asia
SPIA	Solid-phase immunoassay
SpO2	Oxygen saturation

Abbreviation	Full name
TRFIA	time-resolved fluoroimmunoassay
TS	throat swab
UK	United Kingdom
UMICs	Upper middle income countries
UNICEF	United Nations Children's Fund
UR	Uncertainty range
US	United States of America
vsALRI	Very severe acute lower respiratory infection
WHO	World Health Organization
WPR	Western Pacific region
y	year(s)

A2. Search Strategy of IFV

Medline (Ovid)
1. exp Influenza, Human/
2. exp Influenzavirus B/ or exp Influenzavirus A/ or exp Influenzavirus C/
3. *Influenza Vaccines/ or *Influenza A virus/ or *Influenza, Human/ or *Respiratory Tract Infections/ or *Disease Outbreaks/ or *Influenza A Virus, H1N1 Subtype/
4. H1N1pdm.mp
5. pH1N1.mp
6. 2009H1N1.mp
7. exp Bronchiolitis/ or exp Bronchiolitis, Viral/
8. exp Respiratory Tract Diseases/
9. exp Respiratory Tract Infections/ or acute respiratory infections.mp. or Influenza, Human/
10. exp Pneumonia, Viral/ or *Pneumonia/ or acute lower respiratory infections.mp.
11. exp Incidence/
12. exp Prevalence/
13. exp Morbidity/
14. exp Child Mortality/ or exp Infant Mortality/ or *Hospital Mortality/ or exp Mortality/
15. exp Death/ or exp "Cause of Death"/
16. pediatric mortality.mp
17. paediatric mortality.mp
18. pediatric death.mp.
19. paediatric death.mp.
20. burden.mp.
21. (1 or 2 or 3 or 4 or 5 or 6) and (7 or 8 or 9 or 10) and (11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20)
22. animals
23. 21 not 22
24. Limit 23 to (yr="2009–2018" and ("all infant (birth to 23 months)" or "preschool child (2 to 5 years)"))

Embase (Ovid)
1. exp Influenza virus A/ or exp influenza/ or exp Influenza virus A H3N2/ or exp Influenza virus/ or exp Influenza virus A H1N1/ or exp Influenza virus B/
2. exp pandemic influenza/ or exp pandemic
3. influenza outbreak*.mp
4. exp 2009 H1N1 influenza/ or 2009 H1N1.mp
5. H1N1pdm.mp
6. pH1N1.mp
7. exp respiratory tract infection/
8. exp lower respiratory tract infection/
9. exp virus pneumonia/ or exp pneumonia/
10. exp bronchiolitis/ or exp viral bronchiolitis/
11. exp incidence/
12. exp prevalence/
13. exp morbidity/
14. exp mortality/ or exp childhood mortality/ or exp infant mortality/
15. exp death/ or exp child death/
16. paediatric mortality.mp.

17. paediatric mortality.mp.
18. paediatric death.mp.
19. paediatric death.mp.
20. burden.mp.
21. (1 or 2 or 3 or 4 or 5 or 6) and (7 or 8 or 9 or 10) and (11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20)
22. animals
23. 21 not 22
24. Limit 23 to (yr="2009 –2018" and (infant or preschool child <1 to 6 years>))

Global Health (Ovid)
1. exp influenza A/ or exp Influenza A virus/ or exp Influenza B virus/ or exp influenza viruses/ or exp swine influenza A viruses/ or exp swine influenza viruses/ or exp influenza B/ or exp influenza/
2. pandemic influenza.mp
3. 2009 H1N1.mp
4. H1N1pdm.mp
5. pH1N1.mp
6. influenza outbreak*.mp
7. (respiratory diseases or lower respiratory tract infections).sh.
8. exp pneumonia/
9. bronchiolitis.mp.
10. exp incidence/
11. burden.mp.
12. exp morbidity/
13. exp infant mortality/ or exp mortality/
14. exp death/ or exp "causes of death"/
15. paediatric mortality.mp.
16. paediatric mortality.mp.
17. paediatric death.mp.
18. paediatric death.mp.
19. (1 or 2 or 3 or 4 or 5 or 6) and (7 or 8 or 9) and (10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18)
20. Limit 19 to yr="2009–2018"

CINAHL
1. (MH “Influenza, Humans+”) OR (MH “Influenzavirus B+”) OR (MH “Influenzavirus A+”) OR (MM “Influenza, Pamdemic (h1N1)2009”))
2. (MM “Bronchiolitis”) OR (MM “Community–Acquired Pneumonia”) OR (MM “Pneumonia, Viral”) OR (MM “Influenza, Human”)
3. “children”
4. 1 AND 2 AND 3
Limiters: 2009–2018

Web of Science
TOPIC: influenza or 2009 H1N1 or H1N1pdm or pH1N1 AND TOPIC: children AND TOPIC: acute respiratory infection or pneumonia
Time span= 2009–2018

Global Health Library
tw:((tw:(influenza) OR tw:(ph1n1) OR tw:(h1n1pdm) OR tw:(2009 h1n1)) AND (tw:(children)))
AND (db:("WPRIM" OR "LILACS" OR "IMSEAR" OR "IMEMR" OR "WHOLIS") AND
year_cluster:("2009" OR "2010" OR "2011" OR "2012" OR "2013" OR "2014" OR "2015" OR "2016" OR "2017" OR"2018"))

Google
children acute respiratory infections influenza
H1N1pdm OR pH1N1 OR burden OR incidence OR mortality OR morbidity OR death
–animal
filetype:pdf

CNKI (China Knowledge Resource Integrated Database)
Topic: respiratory infection or respiratory tract infection or pneumonia or bronchiolitis
AND Topic: influenza virus or H1N1 or pandemic influenza
AND Topic: morbidity or mortality or disease burden or hospitalization
AND Topic: children or infant
From 1995 to Dec 31 2018.

Wanfang Data
Topic: respiratory infection or respiratory tract infection or pneumonia or bronchiolitis
AND topic: influenza virus or H1N1 or pandemic influenza
AND Topic: morbidity or mortality or disease burden or hospitalization
AND Topic: children or infant
From 1995 to Dec 31 2018.
Chongqing VIP
Title or key words: (children or infant)
AND (morbidity and mortality or mortality cases or hospitalization or disease burden)
AND (influenza virus or H1N1 or pandemic influenza)
AND (respiratory tract infection or respiratory infection or pneumonia or bronchiolitis or lung infection or severe pneumonia or infectious bronchiolitis)
AND (Jan 1 1995 to Dec 31 2018).

A3. Search strategy of hMPV and hPIV

Medline (Ovid)
1. exp Parainfluenza Virus 1, Human/ or exp Parainfluenza Virus 2, Human/ or exp Parainfluenza Virus 3, Human/ or exp Parainfluenza Virus 4, Human/ or exp Parainfluenza virus infection/ or infection, parainfluenza virus.mp. or infections, parainfluenza virus.mp. or virus infection, parainfluenza.mp. or virus infections, parainfluenza.mp. or parainfluenza vaccine.mp. or exp Parainfluenza Vaccines/ or PIV.mp. or HPIV.mp. or Parainfluenza.mp.
2. metapneumovirus.mp. or exp Metapneumovirus/ or hMPV.mp. or HMPV.mp.
3. Bronchiolitis.mp. or Bronchiolitis/ or Bronchiolitis, Viral/
4. exp Respiratory Tract Diseases/
5. exp Respiratory Tract Infections/
6. acute respiratory infections.mp.
7. exp Pneumonia, Viral/ or *Pneumonia/
8. exp Pneumonia, Viral/ or exp Pneumonia/ or Pneumonia.mp.
9. acute lower respiratory infections.mp.
10. exp Incidence/ or exp Prevalence/ or proportion.mp. or Morbidity/ or exp Child Mortality/ or exp Infant Mortality/ or exp Hospital Mortality/ or *Hospital Mortality/ or hospitalization rate.mp. or hospitalisation rate.mp. or exp Death/ or exp "Cause of Death"/ or burden.mp.
11. 1 or 2
12. 3 or 4 or 5 or 6 or 7 or 8 or 9
13. 10 and 11 and 12
14. limit 13 to (humans and ("all infant (birth to 23 months)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)"))
15. limit 14 to yr="1995 –2017"

Embase (Ovid)
1. exp parainfluenza vaccine/ or exp parainfluenza virus infection/ or para influenza virus.mp. or Parainfluenza virus.mp. or parainfluenza viruses.mp. or Parainfluenzavirus.mp. or virus,parainfluenza.mp. or PIV.mp. or hpiv.mp. or exp Paramyxovirinae/
2. exp metapneumovirus/ or exp Metapneumovirus infection/ or mpv.mp. or hmpv.mp.
3. exp respiratory tract infection/ or exp pneumonia/ or exp bronchiolitis/ or exp viral bronchiolitis/
4. exp incidence/ or exp prevalence/ or proportion.mp. or exp morbidity/ or hospitalization rate.mp. or hospitalisation rate.mp. or exp hospital mortality/ or exp mortality/ or exp childhood mortality/ or exp infant mortality/ or exp death/ or exp child death/ or burden.mp.
5. 1 and 3 and 4
6. 2 and 3 and 4
7. limit 5 to (human and (infant <to one year> or preschool child <1 to 6 years>))
8. limit 6 to (human and (infant <to one year> or preschool child <1 to 6 years>))
9. 7 or 8
10. limit 9 to yr="1995 –2017"

Global Health (Ovid)
1. exp parainfluenza/ or exp parainfluenza viruses/ or exp human parainfluenza virus 1/ or exp human parainfluenza virus 2/ or exp human parainfluenza virus 3/ or exp human parainfluenza virus 4/ or HPIV.mp. or PIV.mp.

2. exp metapneumovirus/ or exp human metapneumovirus/ or human metapneumovirus.mp. or metapneumovirus.mp.
3. exp respiratory diseases/ or exp bronchiolitis/ or exp lower respiratory tract infections/ or exp pneumonia/ or (respiratory diseases or lower respiratory tract infections).sh. or exp pneumonia/ or pneumonia.mp. or exp bronchiolitis/ or bronchiolitis.mp.
4. exp incidence/ or proportion.mp. or exp morbidity/ or hospitalization rate.mp. or hospitalisation rate.mp. or exp infant mortality/ or exp neonatal mortality/ or exp mortality/ or exp death/ or exp "causes of death"/
5. 1 or 2
6. 5 and 3 and 4
7. limit 6 to yr="1995 –2017"

CINAHL
TI parainfluenza OR TI HPIV
TI metapneumovirus OR TI HMPV
AND TI acute respiratory infection
AND TI children
1995–2017

Global Health Library
(tw:(parainfluenza)) OR (tw:(piv)) OR (tw:(hpiv)) OR (tw:(metapneumovirus)) OR (tw:(mpv)) OR (tw:(hmpv)) AND (instance:"ghl") AND (limit:("infant" OR "child, preschool" OR "child" OR "newborn"))
1995–2017

Web of Science
TITLE: (parainfluenza) OR TITLE: (HPIV) OR TITLE: (metapneumovirus) OR TITLE: (HMPV)
AND Title= (Acute Respiratory Infections) OR Title= (Pneumonia)
AND TOPIC: (children) OR TOPIC: (child) OR TOPIC: (infant)
1995–2017

CNKI
Topic: respiratory infections or pneumonia or bronchiolitis
And topic: parainfluenza virus or metapneumovirus
And topic: prevalence or deaths or incidence or disease burden or hospitalisation
And topic: children or infant
1995–2017

Wanfang
Topic: respiratory infections or pneumonia or bronchiolitis
And topic: parainfluenza virus or metapneumovirus
And topic: prevalence or deaths or incidence or disease burden or hospitalisation rate
And topic: children or infant
1995–2017

Chongqingvip
Any field: parainfluenza virus or metapneumovirus
AND title or key words: respiratory infection or respiratory tract infection or pneumonia or lung infection or severe pneumonia or bronchiolitis

AND title or key words: incidence or prevalence or death or hospitalisation or burden of disease AND title or key words: children or infant. 1995–2017

A4. Case definitions

Virus refers to any of IFV, hMPV, and hPIV.

For community–based studies:

- Virus–associated ALRI: cough or difficulty breathing with increased respiratory rate for age (cut–offs same as in WHO IMCI case definition) AND laboratory confirmed virus.
- Virus–associated severe ALRI:
  - For 2–59 months: cough or difficulty in breathing with chest wall indrawing AND laboratory confirmed virus;
  - For 0–1 months: increased respiratory rate (over 60 breaths per minute) OR chest wall indrawing AND laboratory confirmed virus.
- Virus–associated very severe ALRI: cough or difficulty breathing with any danger signs (cyanosis, difficulty breastfeeding or drinking, vomiting everything, convulsions, lethargy, or unconsciousness, head nodding) AND laboratory confirmed virus.

For hospital–based studies:

- Hospitalised virus–associated ALRI: physician confirmed diagnosis of ALRI (pneumonia or bronchiolitis) that are hospitalised, or being recommended hospitalisation AND laboratory confirmed virus.
- Hypoxaemia:
  - at altitude <=2500 meters, SpO_2 <90% in children aged 1–59 months and <88% for neonates (at sea level);
  - at altitude >2500 meters, SpO_2 <87% in children aged 1–59 months and <85% for neonates.
- Hospitalised virus–associated ALRI with hypoxaemia: hospitalised ALRI with hypoxaemia (as defined above) AND laboratory confirmed virus.
- Hospitalised virus–associated very severe ALRI: hospitalised ALRI with any danger signs (cyanosis, difficulty in breastfeeding or drinking, vomiting everything, convulsions, lethargy, or unconsciousness, head nodding) OR proxies for very severe disease – requiring mechanical ventilation OR ICU admission AND laboratory confirmed virus.

A5. Assessment tool for risk of bias

Assessment tool for community–based studies

Category	Description	Risk of bias
Study design	Studies where the cases were prospectively enrolled	Low
	Other studies	High
Patient groups excluded	No exclusions that may affect estimates	Low
	Any of the following: 1. Not including very young children (e.g., neonates). 2. Excluding children with high–risk conditions. 3. Other exclusions that may affect estimates	High
Case definition	Using standardised case definitions	Low
	Using non–standardised case definitions	High
Sampling strategy	The proportion of testing is available AND either of the following: 1. At least 90% of eligible cases were tested. 2. Testing a systematic sample of patients.	Low
	Less than 90% of eligible cases were tested OR The proportion of testing is unavailable.	High
Diagnostic test	PCR; Or using other diagnostic tests, but confirming negative samples with PCR	Low
	1. Other diagnostic tests, e.g., culture, IFA, DFA. 2. No mention of diagnostic tests	High

Assessment tool for hospital–based studies

Category	Description	Risk of bias
Study design	Studies where the cases were prospectively enrolled	Low
	Other studies	High
Adjustment for healthcare utilization (only for hospitalisation rate studies)	Either of the following: 1. Including all hospitals or main hospitals; 2. Adjusting for proportion of patients of the catchment area seeking care in other hospitals.	Low
	No related information AND no adjustment for the proportion of patients of the catchment area seeking care in other hospitals.	High
Patient groups excluded	No exclusions that may affect estimates	Low
	Any of the following: 1. Not including very young children (e.g., neonates). 2. Excluding children with high–risk conditions. 3. Other exclusions that may affect estimates	High
Case definition	Using standardised definitions	Low
	Using non–standardised definitions	High
Sampling strategy	The proportion of testing is available AND either of the following: 1. At least 90% of eligible patients were tested. 2. Testing a systematic sample of patients.	Low
	Less than 90% of eligible cases were tested OR The proportion of testing is unavailable.	High
Diagnostic test (only for hospitalisation rate studies)	PCR; Or using other diagnostic tests, but confirming negative samples with PCR	Low
	1. Other diagnostic tests, e.g., culture, IFA, DFA. 2. No information of diagnostic tests	High
Hypoxaemia ascertainment (only for studies with hypoxaemia data)	SpO2 was recorded for all virus–confirmed cases	Low
	SpO2 was recorded for a proportion of virus–confirmed cases.	High

	OR No related information.	

A6. Data imputation – sensitivity analysis

Details of data imputation is presented in Chapter 2. In the previous analysis for IFV, missing rates were imputed using median rate ratios (Nair et al. 2011). Briefly, rates were imputed based on median rate ratios and the data in the reference age group. Unlike the multiple imputation approach, there was one imputed number (one imputed data point) for one study. The results from the median rate ratio approach and the multiple imputation approach are in Table A6–1.

Table A6–1: Pooled incidence rates of IFV–associated respiratory infections for 0–59 months in the community setting using two imputation approaches. [*]

	Excluding imputed data		**Including imputed data (median rate ratio approach)**		**Including imputed data (multiple imputation approach)**
	No[†]	**Rate[‡]**	**No**	**Rate**	**Rate**
IFV–episodes	5	142.9 (69.2–271.9)	8 (3)	135.5 (84–211.3)	175.2 (101.5–302.3)[§]
IFV–ALRI	5	15.4 (10–23.6)	8 (3)	15.8 (10.5–23.9)	15.6 (10.3–22.6)
IFV–severe ALRI	4	2.4 (0.6–9.6)	7 (3)	2.3 (1–5.2)	2.4 (1.0–5.6)
IFV–very severe ALRI	3	0.7 (0.1–3.9)	4 (1)	0.7 (0.2–2.9)	0.7 (0.2–2.7)

[*] Rates in high child mortality countries
[†] No: number of studies. Data in parentheses was the number of imputed studies.
[‡] Rate: per 1,000 children per year. Incidence rate for community-based studies.
[§] A higher rate ratio was estimated between 0–59 m and 0-11 m (or 0–23 m) using the multiple imputation approach compared with the median rate ratio approach. This was mainly driven by one large study in Bangladesh in which the incidence rates of IFV-episodes increased with age. Unlike the median rate ratio, the rate ratio from a meta-analysis was influenced by the sizes of individual studies. Then the higher rate ratio translated to the higher incidence rates after imputation.

Table A6–2. Pooled incidence rates of hMPV–ALRI for 0–59 months including and excluding imputed data*

	Pooled rates with imputed data		Pooled rates without imputed data	
	No of studies	**Rate**	**No of studies**	**Rate**
Low child mortality	4 (3)	22.3 (12.3–40.6)	1	17.5†
High child mortality	5 (1)	21.2 (17.1–26.2)	4	23.0 (19.6–26.9)

Table A6–3. Pooled incidence rates of hPIV–ALRI for 0–59 months including and excluding imputed data‡

	Pooled rates with imputed data		Pooled rates without imputed data	
	No of studies	**Rate**	**No of studies**	**Rate**
Low child mortality	4 (3)	45.5 (22.7–91.0)	1	18.8§
High child mortality	7 (3)	42.5 (31.2–57.8)	4	33.4 (25.4–43.8)

* Using multiple imputation method.
† Only one study reported data for 0-59 months in low child mortality settings.
‡ Using multiple imputation method.
§ Only one study reported data for 0-59 months in low child mortality settings.

A7. Adjustment for under–detection – sensitivity analysis

The details of data scaling are presented in Chapter 2. Table A7–1 shows the hMPV–ALRI hospitalisations estimated by scaling the case number (dividing the observed case number by the proportion of testing). The estimates of hospitalisations were very similar with those in the main analysis.

Table A7–1. Hospitalisation rates of hMPV–ALRI and hospitalisations adjusting for the proportion of testing in the case number.

Age		LMICs	UMICs	HICs	Global estimates by income regions
0–5 m (A)	No. of studies	8	6	5	
	Hospitalisation rate (/1,000)	2.4 (1.6–3.6)	3.2 (1.6–6.6)	3.3 (2.2–5)	
	Hospitalisations (*1,000)	97 (65–145)	54 (27–109)	19 (13–29)	169 (104–282)
6–11 m (B)	No. of studies	7	5	4	
	Hospitalisation rate (/1,000)	2.7 (1.7–4.2)	2.4 (1–5.9)	2.7 (2.2–3.4)	
	Hospitalisations (*1,000)	129 (83–203)	48 (20–117)	19 (15–23)	196 (118–343)
12–59 m (C)	No. of studies	9	8	5	
	Hospitalisation rate (/1,000)	0.6 (0.3–1)	0.4 (0.2–0.8)	0.3 (0.2–0.7)	280 (151–520)
	Hospitalisations (*1,000)	206 (113–375)	59 (29–117)	15 (8–28)	
0–59 m (A+B+C)	Hospitalisations (*1,000)	432 (260–722)	160 (76–342)	53 (36–80)	645 (372–1144)

hCFRs were not adjusted for the under–detection; only tested cases and deaths were included in the analysis. For the three viruses, the hCFR of tested ALRI cases was higher than the hCFR of untested ALRI cases (Table A7–2, A7–3, and A7–4).

Table A7–2. Testing for IFV – the hCFR for tested ALRI cases and the hCFR for untested ALRI cases for 0–59 months using available data.*

Location (Study period)	Tested cases (A1)	Tested deaths (A2)	Untested cases (B1)	Untested deaths (B2)	hCFRs for tested (A=A2/A1, %)	hCFR for untested (C=B2/B1, %)
Kenya; 2010–2014	1156	21	502	21	1.8	6.6
Togo; 2011–2013; 2014–2015	155	2	10	2	1.3	20
South Africa; 1998 to 2005	2602	138	119	138	5.3	26.9
Mozambique; 2011–2014	411	11	11	11	2.7	18.2
Kenya; 2007–2016	2994	102	1102	102	3.4	7.6
Viet Nam; 2008–2013	422	0	0	0	0	NA
Germany; 2010–2014	2630	9	0	9	0.3	NA
Gambia; 2011–2013	626	17	12	17	2.7	41.7
Thailand; 2005–2011	7895	16	21618	16	0.2	0.4
Panama; 2012–2014	912	5	3175	5	0.5	0.8
Argentina; 2008–2010	25	0	0	0	0	NA
South Africa; 2012–2016	206	2	33	2	1	3
Guatemala; 2010–2016	1753	49	405	49	2.8	0.2
Guatemala; 2010–2016	1499	56	289	56	3.7	0.3
Argentina; 2009–2016	4666	59	265	59	1.3	0.4
South Africa; 2015–2017	4400	18	5329	18	0.4	4.6
Morocco; 2010–2011	789	30	0	30	3.8	NA
Zambia; 2011–2013	603	108	14	108	17.9	64.3
South Africa; 2011–2013	917	37	3	37	4	0
Chile; 2012–2013	464	2	17	2	0.4	0
Chile; 2012–2013	679	3	4	3	0.4	0
Meta–estimates					1.3 (0.8–2.1)	3.4 (1.2–9.3)

* NA: not applicable.

Table A7–3. Testing for hMPV – the hCFR for tested ALRI cases and the hCFR for untested ALRI cases for 0–59 months using available data.[*†]

Location	Year	Tested cases (A1)	Tested deaths (A2)	Untested cases (B1)	Untested deaths (B2)	hCFRs for tested (A=A2/A1, %)	hCFR for untested (C=B2/B1, %)
Lusaka, Zambia	2012–2013	590	105	16	9	17.8	56.3
Bamako, Mali	2012–2014	659	100	1	0	15.2	0
Kilifi, Kenya	2011–2013	566	27	2	2	4.8	100
Soweto, South Africa	2011–2013	866	33	8	0	3.8	0
Manhiça, Mozambique	2011–2013	477	6	15	7	1.3	46.7
Soweto, South Africa	2000–2002	1409	66	235	25	4.7	10.6
Kilifi, Kenya	2007–2011; 2013–2016	2758	93	803	79	3.4	6.2
Berlin, Germany	2010–2014	2516	9	9	0	0.4	0
Klerksdorp, South Africa	2010–2015	1259	31	45	2	2.5	4.4
Pietermaritzburg, South Africa	2010–2015	2164	18	52	1	0.8	1.9
Aurora, Colorado, USA	2010–2016	6424	60	9261	18	0.9	0.2
Basse, Gambia	2012–2013	623	17	12	5	2.7	41.7
						2.8 (1.5–5.3)	8.0 (1.9–27.7)

[*] Studies with small number of ALRI deaths (<5 ALRI deaths) were excluded in this analysis. The hCFRs in these studies were very imprecise. Also, very few hMPV-deaths would be missed due to under-detection.

[†] Studies were not included if all ALRI cases were tested.

Table A7–4. Testing for hPIV – the hCFR for tested ALRI cases and the hCFR for untested ALRI cases for 0–59 months using available data.[*†]

Location	Year	Tested cases (A1)	Tested deaths (A2)	Untested cases (B1)	Untested deaths (B2)	hCFRs for tested (A=A2/A1, %)	hCFR for untested (C=B2/B1, %)
Kilifi, Kenya	2007–2011; 2013–2017	2757	93	1270	79	3.4	6.2
Basse, Gambia	2012–2013	623	17	12	5	2.7	41.7
Lusaka, Zambia	2011–2014	590	105	16	9	17.8	56.2
Soweto, South Africa	2011–2013	866	33	8	0	3.8	0
Kilifi, Kenya	2011–2013	566	27	2	2	4.8	100
Bamako, Mali	2012–2014	659	100	1	0	15.2	0
Rabat, Morocco	2010–2011	771	29	18	1	3.8	5.6
Buenos Aires, Argentina	2000–2017	12311	227	1626	25	1.8	1.5
Manhiça, Mozambique	2011–2014	478	12	14	2	2.5	14.3
Soweto, South Africa	1998–2005	2602	138	119	32	5.3	26.9
Klerksdorp, South Africa	2010–2015	1259	31	45	2	2.5	4.4
Pietermaritzburg, South Africa	2010–2015	2164	18	52	1	0.8	1.9
Colorado, United States of America	2010–2016	6424	60	9261	18	0.9	0.2
Berlin, Germany	2010–2014	2512	9	13	0	0.4	0
						3.0 (1.7–5.0)	6.3 (1.9–18.8)

[*] Studies with small number of ALRI deaths (<5 ALRI deaths) were excluded in this analysis. The hCFRs in these studies were very imprecise. Also, very few hPIV-deaths would be missed due to under-detection.
[†] Studies were not included if all ALRI cases were tested.

A8. IFV –sensitivity analysis of morbidity and in–hospital mortality in different stratification groups

Table A8–1 shows the IFV–ALRI hospitalisations in the stratified analysis by World Bank income regions and country development status where available.

Table A8–2 shows the IFV–ALRI in–hospital deaths in the stratified analysis by World Bank income regions and country development status where available.

Table A8–3 shows the IFV–ALRI hospitalisations and in–hospital deaths after excluding pre–2009 data.

Table A8–4 shows the number of IFV–episodes and IFV–ALRI cases in the stratified analysis by country development status.

Table A8–5 shows the incidence of IFV-severe ALRI and IFV-very severe ALRI and the number of cases by child mortality settings.

Table A8–6 shows the hospitalisation rates of IFV–ALRI using the classical random–effect model.

Table A8–1. Hospitalisation rates (per 1,000 children per year) and hospitalisations for IFV–ALRI by World Bank income regions and country development status.*

Age		LMICs	UMICs	HICs	Global estimates by income regions	Developing	Industrialised	Global estimates by development status
0–5 m (A)	No. of studies	13	9	13		24	11	
	Hospitalisation rate (/1,000)	1.8 (1.1–3.1)	3.7 (1.8–7.4)	4.4 (3.1–6.3)		2.8 (1.8–4.3)	3.7 (2.7–5.3)	
	Hospitalisations (*1,000)	80 (48–133)	68 (34–138)	28 (20–40)	176 (101–311)	174 (113–268)	26 (18–36)	200 (131–304)
6–11 m (B)	No. of studies	11	8	9		21	7	
	Hospitalisation rate (/1,000)	1.5 (1–2.4)	3.8 (1.7–8.3)	3.5 (1.4–8.8)		2.7 (1.7–4.3)	2.6 (0.9–7.6)	
	Hospitalisations (*1,000)	66 (43–102)	70 (32–154)	22 (9–55)	158 (83–311)	166 (105–264)	18 (6–52)	185 (111–317)
12–59 m (C)	No. of studies	17	11	20		35	13	
	Hospitalisation rate (/1,000)	0.8 (0.5–1.3)	0.8 (0.3–2)	1.2 (0.6–2.2)		0.9 (0.6–1.5)	0.9 (0.4–1.8)	
	Hospitalisations (*1,000)	274 (171–441)	117 (46–301)	61 (32–116)	452 (248–858)	436 (276–688)	50 (24–106)	486 (300–794)
0–59 m (A+B+C)	Hospitalisations (*1,000)	420 (261–677)	255 (111–593)	111 (60–211)	786 (432–1481)	776 (494–1,220)	94 (48–194)	870 (543–1,415)

* Hospitalisation rates from meta-analysis. Global estimates were the sum of estimates by age and regions.

Table A8–2. The hCFRs (%) and in–hospital deaths of IFV–ALRI by World Bank income regions and country development status.*

Age		LMICs	UMICs	HICs	Global by income regions	Developing	Industrialised	Global by country development status
	No. of studies	10	11	7		23	5	
0–5 m (A)	hCFR (%)	3.2 (0.6–15.4)	2.6 (0.9–7.5)	0.5 (0–4.6)		3.1 (1.3–6.9)	0.3 (0–6.9)	
	Deaths	2,500 (500–13,800)	1,800 (500–6,200)	100 (0–4,100)	4500 (1000–24000)	5,400 (2,100–13,700)	100 (0–2,700)	5,500 (2,100–16,300)
6–11 m (B)	hCFR (%)	8.1 (4.1–15.3)	0.7 (0.1–7.4)	0.8 (0.2–3.2)		2.0 (0.6–6.2)	0.9 (0.2–3.4)	
	Deaths	5,300 (2,400–11,600)	500 (0–4,700)	200 (0–900)	6000 (2500–17200)	3,300 (900–11,500)	200 (0–900)	3,500 (1,000–12,400)
12–59 m (C)	hCFR (%)	3.3 (1.7–6.3)	0.8 (0.3–2.2)	0.4 (0.1–2.1)		1.4 (0.7–2.8)	0.4 (0.1–2.7)	
	Deaths	9,100 (4,000–20,100)	900 (200–3,700)	200 (0–1,300)	10300 (4300–24900)	6,100 (2,700–13,800)	200 (0–1,200)	6,300 (2,700–14,900)
0–59 m (A+B+C)	Deaths	17,000 (6,900–45,100)	3,200 (800–14,400)	600 (100–6,200)	20800 (7800–65700)	14,800 (5,700–39,000)	500 (100–4,800)	15,300 (5,800–43,800)

Table A8–3. The IFV–ALRI hospitalisations and in–hospital deaths after excluding pre–2009 data.

	0–5 m		6–11 m		12–59 m		Burden estimates (hospitalisations or in–hospital deaths) for 0–59 m†
	No ‡	Estimates (rates or hCFRs) §	No	Estimates	No	Estimates	
Hospitalisations							
Low child mortality	9	4.9 (2.4–10)	8	4.8 (1.8–13.2)	14	1.2 (0.5–3.1)	388 (258–585)
High child mortality	15	2.2 (1.4–3.4)	12	1.6 (1.1–2.4)	17	0.6 (0.4–0.9)	443 (185–1073)
Global hospitalisations (*1,000)							832 (443–1658)
in–hospital deaths							
Low child mortality	11	1 (0.2–6.2)	11	0.6 (0–8.1)	11	0.3 (0–2.3)	2500 (200–50800)
High child mortality	16	2.6 (0.8–8.1)	16	2.5 (0.7–9.1)	16	2.2 (1.2–4.1)	9200 (3500–25500)
Global in–hospital deaths							11,600 (3700–76100)

* Hospitalisation rates from meta-analysis. Global estimates were the sum of estimates by age and regions.
† Burden estimates: hospitalisations (*1,000) OR in–hospital deaths.
‡ No: number of studies.
§ Estimates: hospitalisation rates per 1,000 children per year for the analysis of hospitalisations; hCFRs (%) for the analysis of in-hospital deaths.

Table A8–4. The number of IFV–episodes and IFV–ALRI cases for children aged 0–59 months by country development status*

Outcome	Developing	Industrialised	Global
IFV–episodes			
Number of studies	8 (3)	10 (3)	
Incidence rate (/1,000)	175.2 (101.5–302.3)	42.4 (17.2–104.8)	
Number of cases (*1,000)	106,557 (61,943–183,376)	2,953 (1,202–7,259)	109,510 (63,145–190,635)
IFV–ALRI			
Number of studies	8 (3)	4 (3)	
Incidence rate (/1,000)	15.6 (10.3–23.6)	9.3 (7.5–11.5)	
Number of cases (*1,000)	9,498 (6,305–14,313)	648 (524–800)	10,145 (6,829–15,113)

Table A8-5. The incidence of IFV-severe ALRI and IFV-very severe ALRI and the number of cases by child mortality settings. †

		High child mortality
IFV–severe ALRI cases		
0–5 months	Studies	12
	Incidence	5.1 (2.2–11.9)
	Cases (*1,000)	235 (101–544)
6–11 months	Studies	4
	Incidence	6.1 (2.2–16.4)
	Cases (*1,000)	278 (102–756)
12–59 months	Studies	4
	Incidence	1.9 (0.7–5.1)
	Cases (*1,000)	677 (252–1819)
0–59 months	Studies	7 (3)
	Incidence	2.4 (1–5.6)
	Cases (*1,000)	1060 (451–2494)
IFV–very severe ALRI cases		
0–5 months	Studies	4
	Incidence	0.3 (0–13.3)
	Cases (*1,000)	14 (0–697)
6–11 months	Studies	4
	Incidence	1 (0.3–3.5)
	Cases (*1,000)	46 (13–155)
12–59 months	Studies	3
	Incidence	0.5 (0.1–2.3)
	Cases (*1,000)	178 (37–848)
0–59 months	Studies	4 (1)
	Incidence	0.7 (0.2–2.7)
	Cases (*1,000)	306 (78–1209)

Table A8–6. The hospitalisation rate of IFV–ALRI by age and World Bank income regions using the classical random meta–analysis.

Region	0–5 m		6–11 m		12–59 m	
	No‡	Rate §	No	Rate	No	Rate
LMICs	13	2.3 (1.5–3.5)	11	1.7 (1.1–2.7)	17	0.8 (0.5–1.2)
UMICs	9	3.8 (1.4–10.1)	8	3.9 (1.3–11.8)	11	0.8 (0.3–2.4)

* Incidence rate from meta-analysis. Global estimates were the sum of estimates by regions.
† Incidence rate from meta-analysis.
‡ No: number of studies.
§ Rate: hospitalisation rate per 1,000 children per year, derived from meta-analysis.

Global burden of acute lower respiratory infection (ALRI) associated with influenza virus, human metapneumovirus, and human parainfluenza virus among children under five years

Region	0–5 m		6–11 m		12–59 m	
	No‡	Rate §	No	Rate	No	Rate
HICs	13	4.4 (2.6-7.5)	9	3.6 (1.1–11.1)	20	1.2 (0.6–2.6)

A9. hMPV –sensitivity analysis of morbidity and in–hospital mortality in different stratification groups

Table A9–1 shows the hMPV–ALRI hospitalisations in the stratified analysis by World Bank income region and country development status where available.

Table A9–2 shows the hMPV–ALRI in–hospital deaths in the stratified analysis by World Bank income region and country development status where available.

Table A9–3 shows the hMPV–ALRI in–hospital deaths for 2010. Data were included in the analysis if they were from the time points before 2010; or part of the data were from the time points before 2010 (only for studies in which the data were not stratified by years).

Table A9–4 shows the number of hMPV–ALRI cases by country development status.

Table A9–5 shows the number of hMPV–severe ALRI cases in high child mortality settings.

Table A9–1. Hospitalisation rates (per 1,000 children per year) and hospitalisations for hMPV–ALRI by World Bank income regions and country development status*

Age		LMICs	UMICs	HICs	Global estimates by incomes	Developing	Industrialised	Global estimates by development status
0–5 m (A)	No. of studies	8	6	5		16	3	
	Hospitalisation rate (/1,000)	2.4 (1.6–3.5)	3.3 (1.6–7.1)	3.3 (2.2–5.1)		2.7 (1.8–4.1)	3.4 (1.9–6)	
	Hospitalisations (*1,000)	97 (66–143)	55 (26–116)	19 (13–29)	171 (104–288)	153 (101–230)	22 (12–38)	174 (114–268)
6–11 m (B)	No. of studies	7	5	4		13	3	
	Hospitalisation rate (/1,000)	2.7 (1.7–4.3)	2.5 (1.0–5.9)	2.8 (2.2–3.5)		2.5 (1.6–3.9)	2.5 (2.2–2.8)	
	Hospitalisations (*1,000)	129 (82–205)	50 (21–121)	19 (15–24)	199 (118–351)	168 (108–262)	19 (17–21)	187 (125–284)
12–59 m (C)	No. of studies	9	8	5		18	4	
	Hospitalisation rate (/1,000)	0.6 (0.3–1)	0.4 (0.2–0.8)	0.3 (0.2–0.7)		0.5 (0.3–0.7)	0.4 (0.2–0.8)	
	Hospitalisations (*1,000)	206 (113–375)	59 (29–117)	15 (8–28)	280 (151–520)	242 (159–369)	22 (11–44)	264 (170–414)
0–59 m (A+B+C)	Hospitalisations (*1,000)	432 (260–723)	164 (77–354)	54 (36–82)	650 (373–1159)	563 (368–861)	63 (40–104)	626 (409–965)

* Hospitalisation rates from meta-analysis. Global estimates were the sum of estimates by age and regions.

Table A9–2. The hCFRs (%) and in–hospital deaths of hMPV–ALRI by World Bank income regions and country development status*

Age		LMICs	UMICs	HICs	Global by income regions	Developing	Industrialised	Global by country development status
	No. of studies	15	6	7		23	5	
0–5 m (A)	hCFR (%)	4.5 (2.3–8.6)	1.7 (0.6–5.1)	0.4 (0–8.6)		3.2 (1.7–6)	0.4 (0–8.5)	
	Deaths	4300 (2000–9200)	900 (300–3400)	100 (0–3100)	5400 (2300–15700)	4900 (2300–10200)	100 (0–3500)	5000 (2300–13700)
6–11 m (B)	hCFR (%)	0.7 (0–9)	..†	0.6 (0.1–3.9)		0.2 (0–7)	0.6 (0.1–4)	
	Deaths	900 (0–37800)	NA	100 (0–700)	1000 (0–38500)	300 (0–12400)	100 (0–700)	500 (0–13100)
12–59 m (C)	hCFR (%)	0.9 (0.3–2.8)	1.1 (0.1–9.1)	0.5 (0–7)		0.8 (0.2–3.6)	0.3 (0–3)	
	Deaths	1800 (500–6500)	600 (100–6600)	100 (0–2800)	2600 (600–15900)	1900 (400–8500)	100 (0–1700)	2000 (400–10300)
0–59 m (A+B+C)	Deaths	7200 (2600–52300)	1600 (300–10000)	300 (0–6600)	9100 (2900–68800)	7200 (2800–30500)	300 (0–5900)	7500 (2800–36800)

* hCFRs from meta-analysis. Global estimates were the sum of estimates by age and regions.
† All studies reported no MPV-ALRI deaths, so it was impossible to compute hCFR and the number of deaths.

Table A9–3. The hCFRs (%) and in–hospital deaths of hMPV–ALRI for 2010 by the child mortality setting.*†

Age		Low child mortality	High child mortality	Global estimates by child mortality settings
0–5 m (A)	No. of studies	6	4	
	hCFR (%)	0.9 (0.2–3.5)	2.9 (0.9–8.5)	
	Deaths	600 (100–2600)	6100 (1700–21200)	6600 (1800–23800)
6–11 m (B)	No. of studies	6	4	
	hCFR (%)	2.2 (0.5–8.2)	..‡	
	Deaths	1300 (300–5000)	NA	1300 (300–5000)
12–59 m (C)	No. of studies	9	4	
	hCFR (%)	0.9 (0.3–2.8)	0.3 (0.0–2.4)	
	Deaths	900 (100–7400)	700 (0–15600)	1600 (100–22900)
0–59 m (A+B+C)	Deaths	2800 (500–15100)	6800 (1700–36800)	9600 (2300–51200)

Table A9–4. The incidence and number of hMPV–ALRI cases for 0–59 months by World Bank income regions and country development status. §

	LMICs	UMICs	HICs	Global by income regions	Developing	Industrialised	Global by country development status
No. of studies	4 (1)	2 (1)	3 (2)		6 (2)	3 (2)	
Incidence rates (/1,000)	20.1 (15.5–26.1)	17.7 (9.9–31.8)	27.4 (14.6–51.3)		19.5 (15–25.3)	27.4 (14.6–51.3)	
Cases (*1,000)	8669 (6690–11235)	3253 (1821–5812)	1737 (931–3241)	13658 (9442–20288)	11837 (9108–15387)	1907 (1023–3559)	13744 (10130–18946)

* Only the hospitalisation rate and hCFR data before 2010 (or partly before 2010) were included in this analysis. The population estimates for 2010 were used.

† hCFR from meta-analysis. Global estimates were the sum of estimates by age and regions.

‡ All studies reported zero MPV-ALRI death for this strata, so it was impossible to compute hCFR and the number of deaths.

§ Incidence rates from meta-analysis. Global estimates were the sum of estimates by regions.

Table A9–5. The incidence rates and number of hMPV–severe ALRI cases for 2018 in high child mortality setting. *

Age		High child mortality
0–5 m	No. of studies	4
	Incidence rate (/1,000)	9.7 (1.5–58.1)
	Cases (*1,000)	446 (72–2,752)
6–11 m	No. of studies	3
	Incidence rate (/1,000)	13.7 (3.5–51.6)
	Cases (*1,000)	625 (164–2,383)
12–59 m	No. of studies	3
	Incidence rate (/1,000)	5.9 (2.2–15.8)
	Cases (*1,000)	2,104 (789–5,609)
0–59 m	No. of studies	4 (1)
	Incidence rate (/1,000)	5.3 (1.6–17.9)
	Cases (*1,000)	2,375 (715–7,896)

* Incidence rates from meta-analysis.

A10. hPIV –sensitivity analysis of morbidity and in–hospital mortality in different stratification scenarios

Table A10–1 shows the hPIV–ALRI hospitalisations in the stratified analysis by World Bank income regions and country development status where available.

Table A10–2 shows the hPIV–ALRI in–hospital deaths in the stratified analysis by World Bank income regions and country development status where available.

Table A10–3 shows the incidence and number of hPIV-ALRI cases for 0–59 months by country development status.

Table A10–4 shows the incidence and number of hPIV–severe ALRI cases in high child mortality settings.

Table A10–1. Hospitalisation rates (per 1,000 children per year) and hospitalisations for hPIV–ALRI by World Bank income regions and country development status *

Age		LMICs	UMICs	HICs	Global estimates by income regions	Developing	Industrialised	Global estimates by development status
0–5 m (A)	No. of studies	7	6	4		14	3	
	Hospitalisation rate (/1,000)	3.8 (1.8–7.8)	5.7 (3–10.5)	5.5 (3.1–9.9)		4.9 (3–7.9)	3.7 (3–4.5)	
	Hospitalisations (*1,000)	168 (81–349)	105 (56–196)	35 (20–62)	308 (157–607)	304 (188–493)	26 (21–32)	330 (209–524)
6–11 m (B)	No. of studies	7	5	3		13	2	
	Hospitalisation rate (/1,000)	3.5 (1.7–7)	3.8 (1.9–7.6)	3.5 (1.9–6.5)		3.8 (2.4–6.1)	2.5 (1.7–3.7)	
	Hospitalisations (*1,000)	154 (76–311)	70 (35–139)	22 (12–41)	246 (123–491)	234 (147–373)	17 (12–26)	252 (159–398)
12–59 m (C)	No. of studies	8	8	4		19	1	
	Hospitalisation rate (/1,000)	0.8 (0.4–1.4)	0.8 (0.4–1.6)	0.8 (0.2–2.9)		0.8 (0.5–1.3)	..	
	Hospitalisations (*1,000)	274 (147–512)	117 (59–233)	41 (11–153)	432 (217–898)	388 (241–623)	..	..
0–59 m (A+B+C)	Hospitalisations (*1,000)	596 (304–1171)	292 (150–569)	98 (42–257)	986 (497–1997)	926 (576–1489)	..	..

* Hospitalisation rates from meta-analysis. Global estimates were the sum of estimates by age and regions.

Table A10–2. The hCFRs (%) and in–hospital deaths of hPIV–ALRI by World Bank income regions and country development status.*

Age		LMICs	UMICs	HICs	Global by country income regions	Developing	Industrialised	Global by country development status
	No. of studies	15	8	4		25	2	
0–5 m (A)	hCFR (%)	3.9 (2.1–7.3)	2.4 (1.3–4.6)	0.9 (0.2–3.6)		3.2 (2.0–5.0)	1.0 (0.3–3.9)	
	Deaths	6600 (2600–17000)	2500 (1100–6100)	300 (100–1500)	9400 (3700–24500)	9700 (5100–18900)	300 (100–900)	10000 (5200–19600)
6–11 m (B)	hCFR (%)	3.5 (2.2–5.6)	1.9 (0.8–4.1)	0.9 (0.4–1.9)		2.6 (1.2–5.8)	1.3 (0.3–4.9)	
	Deaths	9600 (4500–20900)	2200 (800–6400)	400 (100–1700)	6000 (1900–20800)	6100 (2400–14900)	200 (100–900)	6300 (2500–15900)
12–59 m (C)	hCFR (%)	2 (0.5–7.4)	3.8 (2.2–6.6)	1.2 (0.3–4.7)		2.7 (1.8–4.1)	0.9 (0.4–2.0)	
	Deaths	3100 (700–13800)	2700 (1100–6400)	300 (100–1200)	12200 (5300–28800)	10500 (5600–19500)	..†	..
0–59 m (A+B+C)	Deaths	19400 (7800–50800)	7400 (3000–18900)	1000 (200–4100)	27800 (11000–73700)	26400 (13300–53000)	..	..

* hCFRs from meta-analysis. Global estimates were the sum of estimates by age and regions.
† There was only one study with hPIV-ALRI hospitalisation rates, thus it was impossible to estimate the hPIV-ALRI hospitalisations and in-hospital deaths.

Table A10–3. The incidence and number of hPIV-ALRI cases for 0–59 months by country development status.*

	Developing	Industrialised	Global by country development status
No. of studies	7 (3)	4 (3)	
Incidence (/1,000)	42.5 (31.2-57.8)	45.5 (22.7-91)	
Cases (*1,000)	25837 (19005-35133)	3165 (1587-6315)	29002 (20592-41448)

Table A10–4. The incidence and number of hPIV–severe ALRI cases in high child mortality settings. †

Age		High child mortality
0–5 m	No. of studies	4
	Incidence rate (/1,000)	20.6 (2.8–134.8)
	Cases (*1,000)	948 (138–6512)
6–11 m	No. of studies	3
	Incidence rate (/1,000)	30.7 (8.3–106.6)
	Cases (*1,000)	1400 (393–4985)
12–59 m	No. of studies	3
	Incidence rate (/1,000)	8.1 (2.2–29.8)
	Cases (*1,000)	2887 (790–10557)
0–59 m	No. of studies	5 (2)
	Incidence rate (/1,000)	9.3 (3.5–24.9)
	Cases (*1,000)	4190 (1585–11083)

* Incidence rates from meta-analysis. Global estimates were the sum of estimates by regions.
† Incidence rates from meta-analysis.

A11. Estimating hospitalisations of hMPV–ALRI and hPIV–ALRI using the proportion–based approach

Table A11–1. The proportion of hospitalised hMPV–ALRI for 0–59 months by World Bank income regions.

	No. of studies	Proportion (%) for 0–59 m
All studies with data for 0–59 months	78	5.8 (5.0–6.6)
By World Bank income regions		
Low income	4	6.5 (5.3–7.9)
Middle income	59	5.6 (4.8–6.5)
High income	15	6.2 (4.5–8.5)

Table A11–2. The proportion of hospitalised hPIV–ALRI for 0–59 months by World Bank income regions.

	No. of studies	Proportion (%) for 0–59 m
All studies with data for 0–59 months	91	8.7 (7.5–10.2)
By World Bank income regions		
Low income	4	11.1 (6.1–19.3)
Middle income	70	9.1 (7.5–10.9)
High income	17	6.7 (5.3–8.5)

Table A11–3. The hospitalisations of hMPV–ALRI and hPIV–ALRI for 0–59 months using the proportion–based approach.

	No. of studies	Proportion (%) of virus–ALRI for 0–59 m	Hospitalisations of all–cause ALRI (*1,000)	Hospitalisations of virus–ALRI (*1,000)*
hMPV	78	5.8 (5.0–6.6)	5,133–16,400 (McAllister et al. 2018, Troeger et al. 2018)	298 – 951
hPIV	91	8.7 (7.5–10.2)		447 – 1,427

* Estimated by applying the point proportion of virus–ALRI to the ranges of hospitalisations of ALRI.

A12. Estimating IFV–associated ALRI overall mortality – sensitivity analysis

The main approach to estimate IFV–ALRI overall deaths is detailed in Chapter 4. Details of two alternative approaches used for IFV – Approach IFV 2 and Approach IFV 3 – are presented here. As summarised in Chapter 4, the final aim of Approach IFV 2 and 3 was to estimate the inflation factor between overall IFV–ALRI mortality and the in–hospital mortality. Approach IFV 2 and 3 consisted of three steps: (1) estimating the proportion of ALRI deaths that were associated with IFV for a given country; (2) estimating the overall IFV–ALRI deaths using the proportion; (3) estimating the inflation factor. The two approaches were the same in Step (2) and (3). Details of Step (1) of the two approaches are presented.

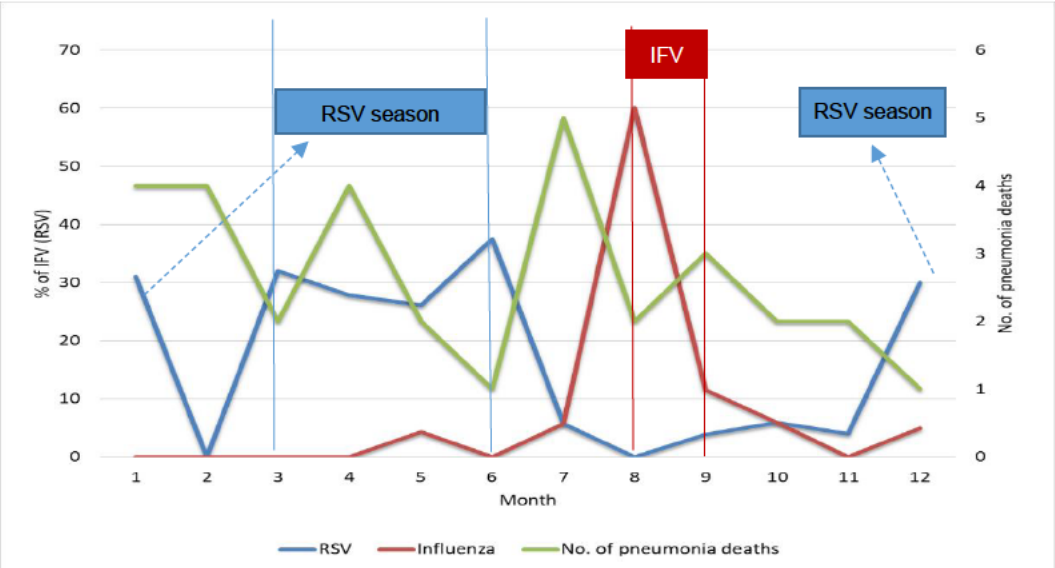

Figure A12–1. One example to show the details of the first step of Approach IFV 2.

Step (1) of Approach IFV 2: the proportion of virus–ALRI deaths in total ALRI deaths

IFV (RSV) season was defined as at least 10 samples were tested and at least 10% of tested samples were positive. The months outside IFV and RSV seasons were the "baseline" months. The average pneumonia deaths during the "baseline" period were the "baseline" deaths. The IFV–associated deaths at a given site were the excess deaths in IFV season compared with the "baseline" deaths. The proportion of IFV–associated deaths in all pneumonia deaths was estimated at a given site. The assumption was that the degree of association between the virus activity and the number of virus–associated pneumonia deaths was the same for IFV and RSV. In other words, the CFR of IFV cases was the same with that for RSV. However, the temporal association between influenza activity and the number of pneumonia deaths might be confounded by other pathogens and factors. This model used influenza activity data mainly to define "season" and "baseline" period (except when the IFV season and the RSV season overlapped), so this model is less affected by the accuracy of the percent positivity of IFV.

The proportion of IFV–ALRI deaths was then estimated using the total number of modelled IFV–ALRI deaths across years and the total number of ALRI deaths. Other details of the estimation using Approach IFV 2 is in Table A12–1.

Table A12–1. Estimating the IFV–ALRI overall mortality using Approach IFV 2. *

Year	Country	IFV-PNE death at the site (a)	PNE death at the site (b)	Proportion of IFV-PNE deaths (c=a/b, %)	U5 PNE deaths (d) (Liu et al. 2016)	Overall IFV-ALRI deaths (e = d*c)	IFV-ALRI in-hospital deaths (f)	Inflation factor (h = e/f)	Median inflation factor	Global overall IFV-ALRI mortality†
2010-2012	Bangladesh	-33.2	208	--	17408	--	361	--	3.0	36100 (UR 14300-121000)
2010-2015	South Africa	4.6	125	3.7	7105	264	98	2.7		
2012-2016	Mozambique	4.5	151	3.0	11769	351	104	3.4		
2008; 2010-2015	Kenya (Nairobi)	-13.5	244	--	10584	--	142	--		
2010-2016	Kenya (Siaya)	50.1	1261	4.0	10584	421	142	3.0		

The IFV–ALRI in–hospital deaths for a given country (f) were estimated using the location–matched hospitalisation rate and hCFR data (site–matched data in Siaya, Kenya and Manhiça, Mozambique; country–matched data in South Africa). For Bangladesh, we used the hCFR meta–estimate in developing countries because site– or country–matched data were unavailable (Table A12–2). Estimation was done as shown in the following formula:

Country IFV–ALRI in–hospital deaths = $\mathrm{U5\ population} * \mathrm{U5\ Hos\ Rate} * \mathrm{U5\ hCFR}$

Table A12–2: In–hospital deaths data and population–based pneumonia deaths data by site

Site and period (population–based pneumonia deaths and IFV activity)	Site and period (in–hospital IFV–ALRI deaths) (f)
Nairobi (Kenya), 2008, 2010–2015	Siaya (Kenya), 2010–2014
Siaya (Kenya), 2010–2016	Siaya (Kenya), 2010–2014
Bangladesh, 2010–2012	Meta–estimates in developing countries
Manhiça, Mozambique, 2012–2016‡(Nguenha et al. 2018)	Manhiça, Mozambique, 2011–2014
Agincourt, South Africa, 2010–2015	Paarl, Soweto, Klerksdorp, Pietermaritzburg, 2010–; Soweto, 1998–2005

* PNE: pneumonia. IFV: influenza virus. U5: children under five years.

† Estimated by summing up overall mortality in developing (inflation factor = 3.0) and industrialised countries (inflation factor = 1.6)

‡ Local IFV and RSV activity data in Manhiça, Mozambique were available during Jan 2012-June 2014, but unavailable during July 2014-Dec 2016. For IFV, we used the data in neighbouring areas (distance <100 kilometres). For RSV, the average proportions of RSV during Jan 2012-Dec 2013 were extrapolated to Jan-Dec 2014.

Step (1) of Approach IFV 3: the proportion of virus–ALRI deaths in total ALRI deaths

The proportion of IFV–ALRI deaths in total ALRI deaths was estimated using the following formula:

$$\%\ IFV\ in\ ALRI\ deaths =$$

$$\sum_{1}^{\mathrm{k}}\left(\frac{\mathrm{PropIFVi} * \mathrm{RiskDeathIFV}}{(\mathrm{PropIFVi} * \mathrm{RiskDeathIFV} + (1 - \mathrm{PropIFVi}) * 1.00} * \mathrm{MonPNEi}\right) / \sum_{1}^{\mathrm{k}}\mathrm{MonPNEi}$$

Using Approach IFV 3, the CFR for IFV–ALRI was considered to be constant throughout a year. The samples at data–existing sites were mostly from children under five years with severe acute respiratory infections; the proportion of IFV in these samples considered a proxy of that in ALRI cases. The risk of death from IFV compared with non–IFV–ALRI was 0.56 (1.9/3.4) according to (1) the hCFR of IFV–ALRI versus the hCFR of non–IFV–ALRI using data from eight hospital–based studies in low– and middle–income countries (1.9 [95%CI 0.5–6.6)] vs 3.4 [95%CI 1.6–7.3], Table A12–4 and Table A12–5). For this approach, the bias mainly came from the ratio of case–fatality of IFV–ALRI to non–IFV–ALRI. Alternative estimates of this ratio were not identified in published reports. The variation in observed influenza activity between months was assumed to be generalisable to children who were not tested. Moreover, it was assumed that the testing practice remained stable throughout a year. Other details of the estimation using Approach IFV 3 is in Table A12–3.

Table A12–3. Estimating the overall IFV–ALRI mortality using Approach IFV 3*

Year	Country	IFV-PNE death at the site (a)	PNE death at the site (b)	Proportion of IFV-PNE deaths (c=a/b, %)	U5 PNE deaths (d) (Liu et al. 2016)	Overall IFV-ALRI deaths (e = d*c)	IFV-ALRI in-hospital deaths (f)	Inflation factor (h = e/f)	Median inflation factor	Global overall IFV-ALRI mortality†
2010-2012	Bangladesh	8.6	208	4.1	17408	720	361	2.0	4.1	48000 (UR 19300-150100)
2010-2015	South Africa	5.4	125	4.3	7105	307	98	3.1		
2012-2016	Mozambique	5.9	151	3.9	11769	460	104	4.4		
2008; 2010-2015	Kenya (Nairobi)	14.6	244	6.0	10584	633	142	4.5		
2010-2016	Kenya (Siaya)	69.8	1261	5.5	10584	586	142	4.1		

Table A12–4. hCFR meta–estimates for IFV–positive ALRI cases, IFV–negative ALRI, and for untested ALRI cases. ‡

	hCFR in IFV cases (%)	hCFR in IFV negative cases (%)	hCFR in non–test cases (%)	hCFR in all non–IFV cases (%)
0–5 m	1.1 (0.1–19.4)	5.0 (2.5–10.0)	10.4 (1.9–41.1)	5.5 (2.8–10.5)
6–11 m	3.1 (0.8–11.0)	3.1 (1.2–8.1)	11.1 (0.9–62.9)	3.7 (1.6–8.5)
12–59 m	1.4 (0.4–5.6)	1.4 (0.5–3.9)	16.4 (2.5–59.9)	2.0 (0.8–4.8)
0–59 m	1.9 (0.5–6.6)	2.8 (1.2–6.5)	13.5 (3.1–43.7)	3.4 (1.6–7.3)

* PNE: pneumonia. IFV: influenza virus. U5: children under five years.
† Estimated by summing up overall mortality in developing (inflation factor = 3.4) and industrialised countries (inflation factor = 1.6)
‡ Meta-estimates were based on the data in eight studies in low- and middle-income countries providing relevant data by three age bands and testing >=90% of eligible ALRI cases.

Table A12–5. Tested/untested hospitalised ALRI cases/deaths in eight studies in low– and middle–income countries with available data.*

Location (Study period)	Age	IFV–ALRI deaths	IFV–ALRI cases	IFV-negative ALRI deaths	IFV-negative ALRI cases	Untested ALRI deaths	Untested ALRI cases
Gambia; 2011–2013	0–5 m	0	17	5	239	0	3
Morocco; 2010–2011	0–5 m	0	3	14	125	0	0
Mozambique; 2011–2014	0–5 m	0	5	5	108	0	1
South Africa; 1998 to 2005	0–5 m	1	28	92	934	17	42
South Africa; 2011–2013	0–5 m	0	18	17	437	0	3
Thailand; 2005–2011	0–5 m	0	34	5	669	26	1961
Togo; 2011–2013; 2014–2015	0–5 m	0	1	2	33	1	5
Zambia; 2011–2013	0–5 m	3	11	58	310	4	6
Gambia; 2011–2013	6–11 m	0	4	5	135	2	5
Morocco; 2010–2011	6–11 m	0	9	8	126	0	0
Mozambique; 2011–2014	6–11 m	1	7	2	90	0	4
South Africa; 1998 to 2005	6–11 m	2	20	24	585	5	21
South Africa; 2011–2013	6–11 m	1	15	13	211	0	0
Thailand; 2005–2011	6–11 m	0	110	3	1437	22	3846
Togo; 2011–2013; 2014–2015	6–11 m	0	5	0	18	0	2
Zambia; 2011–2013	6–11 m	1	7	28	139	3	3
Gambia; 2011–2013	12–59 m	0	12	7	219	3	4
Morocco; 2010–2011	12–59 m	1	16	7	510	0	0
Mozambique; 2011–2014	12–59 m	0	11	3	190	2	6
South Africa; 1998 to 2005	12–59 m	1	50	18	985	10	56
South Africa; 2011–2013	12–59 m	1	21	5	239	0	0
Thailand; 2005–2011	12–59 m	1	559	7	5086	30	15811
Togo; 2011–2013; 2014–2015	12–59 m	0	14	0	84	1	3
Zambia; 2011–2013	12–59 m	2	13	21	144	2	5

* Only including studies testing >=90% of ALRI cases.

A13. Adjustment for missing hPIV–4.

Since a mix of three–type (hPIV–1 to hPIV–3) and four–type (hPIV–1 to hPIV–4) data were included, incidence rates, hospitalisation rates, proportions, and hCFRs were adjusted to account for the missing hPIV–4 at study levels as presented in Chapter 6. Two key parameters used in the adjustment were estimated in Table A13–1 and Table A13–2. Table A13–3 shows the unadjusted estimates and the adjusted estimates for each outcome.

Table A13–1. The prevalence of each hPIV type for children aged 0–59 months.*

	High child mortality	Low child mortality	All studies
No. of studies	16	9	25
Prevalence of hPIV–1 (%)	29.1 (23.7–35)	21.0 (14.4–29.6)	26.1 (21.6–31.2)
Prevalence of hPIV–2 (%)	10.7 (7.5–14.9)	6.3 (2.8–13.5)	8.9 (6.2–12.6)
Prevalence of hPIV–3 (%)	47.2 (40.3–54.1)	57.3 (46.5–67.5)	50.6 (44.4–56.8)
Prevalence of hPIV–4 (%)	12.3 (7.3–19.8)	11.8 (7.3–18.4)	12.2 (8.5–17.2)

Table A13–2. The prevalence of each hPIV type in hPIV–ALRI deaths for children aged 0–59 months.†

	Prevalence in cases (%)	hCFR (%)	Prevalence in deaths (%)
hPIV–1	26.1	9.4 (5.4–15.8)	35.7
hPIV–2	8.9	9.1 (3.8–20.1)	11.4
hPIV–3	50.6	6.0 (3.4–10.3)	47.1
hPIV–4	12.2	3.7 (0.6–19.1)	5.7

Based on the prevalence of four hPIV types and the ratio of case–fatality of hPIV–4 to the other three types, hPIV–4 was estimated to account for about 6% of hPIV–associated ALRI deaths, and hPIV–1 to hPIV–3 for 94% of hPIV–associated ALRI deaths.

Table A13–3. The unadjusted and adjusted burden estimates of hPIV–ALRI for children under five years by outcome.‡

	Unadjusted burden estimates	Adjusted burden estimates
Global hPIV–ALRI cases in the community (*1,000) Global hPIV–ALRI hospitalisations (*1,000)	25,649 (UR 18,284–38,000)	29,478 (UR 19,240–46,714)
Using the incidence–based approach	947 (UR 561–1,644)	1,007 (UR 601–1,750)
Using the proportion–based approach	411–1,312	447–1,427
Global hPIV–ALRI in–hospital deaths	26,400 (UR 12,300–58,300)	25,700 (UR 12,000–56,500)

* Data were from hospital-based studies; data were eligible if there were at least five hPIV-ALRI cases, and four hPIV types were detected.
† Data were from five hospital-based studies where at least 90% of cases were tested, and there were at least five hPIV-positive ALRI deaths. Data were from Zambia, South Africa, Mali, Morocco, Philippines.
‡ Data were adjusted to account for missing hPIV–4 in incidence rates, hospitalisation rates and hCFRs.

A14. Sensitivity analysis of hMPV–associated and hPIV–associated ALRI overall mortality in high child mortality settings

In sensitivity analysis, overall hMPV– and hPIV–ALRI mortality in high child mortality settings were estimated using the following formula:

$$\text{Overall virus\_ALRI mortality} = \%virus\ in\ ALRI\ deaths * ALRI\ deaths$$

hMPV–ALRI overall deaths

The proportion of hMPV in ALRI deaths was estimated using data from 13 hospital–based studies (including five PERCH sites) from the high mortality setting, in which at least 90% of ALRI cases were tested and at least five ALRI deaths were enrolled during the study period. Although 19% ALRI deaths occurred among neonates, no hMPV deaths were reported in hospital–based studies. Thus, the percent of hMPV in ALRI deaths was only estimated for 1–59 months, and applied to the number of ALRI deaths for the corresponding age band (i.e., 1–59 m).

hPIV–ALRI overall deaths

The proportion of hPIV positives in ALRI deaths was estimated using data from 12 hospital–based studies (including five PERCH sites) from high mortality settings in which at least 90% of ALRI cases were tested and at least five ALRI deaths were identified. All the 12 studies detected four hPIV types. In these studies, neonatal hPIV–ALRI deaths were identified. The percent of hPIV was estimated for the overall age band (i.e., 0–59 months) as the data were insufficient to allow disaggregation by narrower age bands (e.g., 0–27 d and 1–59 m).

Table A14–1. Estimating the overall virus–associated ALRI mortality in high child mortality settings using "the proportion of virus detected in ALRI deaths".

	Virus–ALRI deaths (A)	ALRI deaths (B)	% of virus in ALRI deaths (C)	2017 ALRI deaths for high child mortality settings (D)	Overall virus–ALRI deaths for high child mortality settings (E=C*D)
hMPV*†	18	573	3.2% (95%CI 1.9–5.2)	622,742 for 1–59 m	19,900 (UR 12,100–33,200) for 1–59 m
hPIV‡	42	584	7.3% (95%CI 4.6–11.3)	769,712 for 0–59 m	56,100 (UR 36,500–87,400) for 0–59 m

* A meta–analysis was conducted to combine data from 13 studies from Morocco, Philippines, Bangladesh, Gambia, Zambia, Mali, Kenya, South Africa, and Mozambique. The percent was 3.4% (95%CI 1.8–6.1) when pooling five PERCH sites in Gambia, Zambia, Mali, Kenya, and South Africa.

† The percent of hMPV was estimated for 1–59 m, and only used to yield the hMPV–ALRI deaths for 1–59 m.

‡ A meta–analysis was performed to combine data from 12 studies from Philippines, Bangladesh, Gambia, Zambia, Mali, Kenya, South Africa, and Mozambique. The pooled percent was 9.4% (95%CI 6.6–13.3) when only pooling five PERCH sites in Gambia, Zambia, Mali, Kenya, and South Africa.

A15. Estimating the attributable fraction for virus–associated ALRI cases

Table A15–1. The odds ratios for virus and virus–associated ALRI cases and the corresponding attributable fraction (AF).

	Odds ratios (ORs)	**Attributable fraction [AF% = (OR–1) *100/OR]***
IFV	5.1 (Shi et al. 2015); 2.8–3.3 (Pneumonia Etiology Research for Child Health Study Group (PERCH) 2019); 55.2 for IFVA and 3.3 for IFVB (Benet et al. 2017)	80%
hMPV	3.8 (Shi et al. 2015); 4.6 (Pneumonia Etiology Research for Child Health Study Group (PERCH) 2019); 11.0 (Benet et al. 2017)	78%
hPIV	3.4 (Shi et al. 2015)	71%
hPIV–1	7.5 (Pneumonia Etiology Research for Child Health Study Group (PERCH) 2019, Benet et al. 2017)	87%
hPIV–2	Not significant (1.0–2.0) (Pneumonia Etiology Research for Child Health Study Group (PERCH) 2019, Benet et al. 2017)	25%
hPIV–3	2.6 (Pneumonia Etiology Research for Child Health Study Group (PERCH) 2019); 6.7 (Benet et al. 2017)	79%
hPIV–4	1.7 (Pneumonia Etiology Research for Child Health Study Group (PERCH) 2019); 2.6 (Benet et al. 2017)	55%

Table A15–2. Estimating the average attributable fraction (AF) for hPIV–ALRI.

	AF*i* (%)†	**Prevalence of hPIV*i*‡**	**Average AF (%) =** $\sum_i^4 \% \, \boldsymbol{hPIVi} * \boldsymbol{AFi}$
hPIV1	87%	26%	73%
hPIV2	25%	9%	
hPIV3	79%	52%	
hPIV4	55%	12%	

* Input OR was the median value of ORs in published multi-country studies.
† The AFs for each hPIV type are in Table A15-1.
‡ The estimation of the prevalence of each hPIV type is in Appendix A13.

A16. Estimating the virus–attributable ALRI deaths in high child mortality settings using CHAMPS data

In sensitivity analysis, the virus–attributable ALRI deaths in high child mortality settings were estimated using data from Child Health and Mortality Prevention Surveillance (CHAMPS). The input data for this analysis and the results are in Table A16–1. Deaths occurring during December 2016–October 2019 were included in the analysis for hMPV and hPIV; deaths occurring during December 2016–December 2019 were analysed for IFV.

Table A16–1. Estimating the virus–attributable ALRI deaths using CHAMPS data.

Virus	Age	Virus–ALRI deaths (A)*	ALRI deaths (B)†	% of virus–attributable ALRI (C=A*100/B)	2017 ALRI deaths for high child mortality settings (D)	Virus–attributable ALRI deaths for high child mortality settings (E=C*D/100)
IFV‡	0–27 days	1	93	1.0 (0.2–5.8)	146,967	1,500 (UR 300–8,100)
	1–59 months	6	200	3.0 (1.1–6.4)	622,742	18600 (UR 7,800–45,600)
	0–59 months					20,100 (UR 8,100–53,700)
hMPV§	0–27 days	0	91	..	146,967	..
	1–59 months	3	191	1.6 (0.3–3.5)	622,742	9,900 (UR 2,600–39,300)
	0–59 months					..
hPIV**	0–27 days	2	91	2.2 (95%CI 0.3–7.7)	146,967	3,200 (UR 700–16,800)
	1–59 months	13	191	6.8 (95%CI 3.7–11.4)	622,742	42,300 (UR 24,300–74,900)
	0–59 months					45,500 (UR 24,900–91,700)

* Virus as any of immediate, co-morbid, and underlying cause of death (virus appeared anywhere in the causal chain of deaths).
† ALRI as any of immediate, co-morbid, and underlying cause of death (ALRI appeared anywhere in the causal chain of deaths).
‡ Deaths occurring during Dec 2016-Dec 2019.
§ Deaths occurring during Dec 2016-Oct 2019.
** Deaths occurring during Dec 2016-Oct 2019.

A17. Yearly variation in hospitalisation rates of virus–associated ALRI

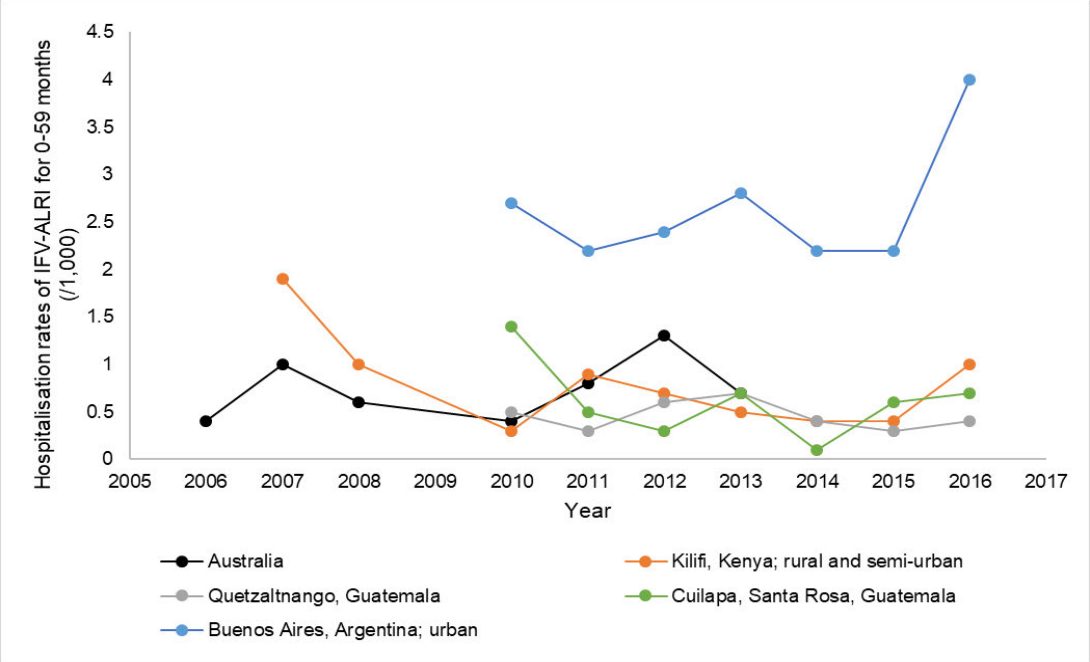

Figure A17–1. Annual hospitalisation rates of IFV–ALRI in multi–year studies

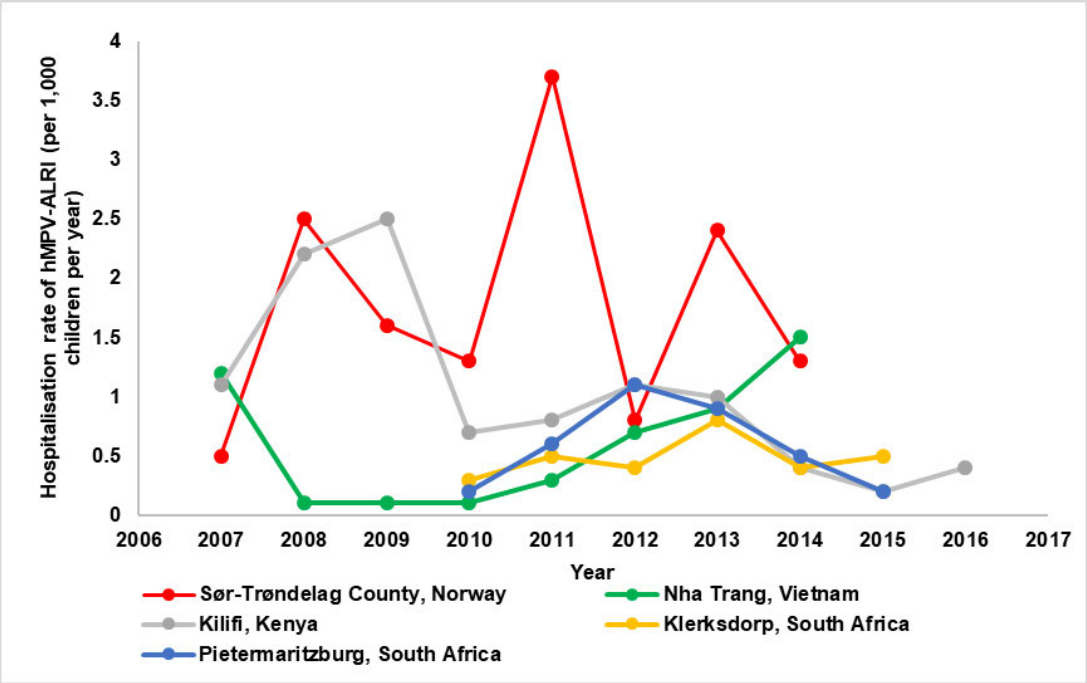

Figure A17–2. Annual hospitalisation rates of hMPV–ALRI in multi–year studies

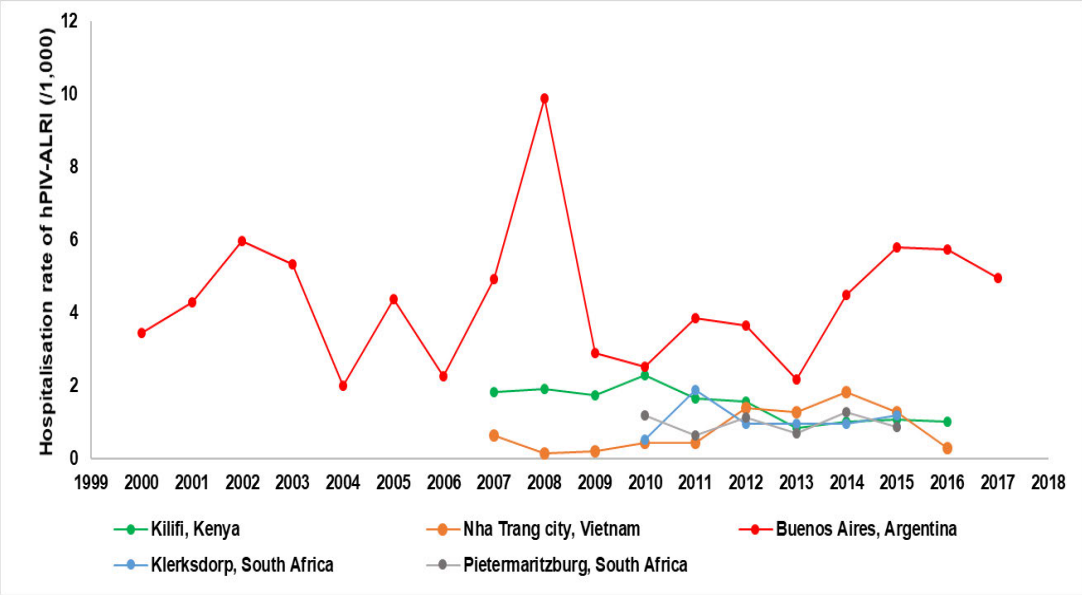

Figure A17–3. Annual hospitalisation rates of hPIV–ALRI in multi–year studies

A18. Characteristics of included studies by outcome

Table A18–1a. IFV – the number of included studies with incidence rates (N = 38)

	IFV–episodes (No.)	IFV–ALRI (No.)	IFV–severe ALRI (No.)	IFV–very severe ALRI (No.)
All studies	27	12	14	4
New studies (not in the previous analysis)	21	7	5	4
From the collaboration network	9	10	12	4
0–59 months*	18 (6)	12 (6)	7 (3)	4 (1)
Developing countries	14	8	14	4
World Bank income region†				
LICs	8	0	2	0
LMICs	5	7	11	3
UMICs	1	1	1	1
HICs	13	4	0	0
WHO region‡				
AFR	5	1	2	1
AMR	4	2	1	1
EMR	0	1	3	0
EUR	5	2	0	0
SEAR	7	5	8	2
WPR	6	1	0	0
After the 2009 influenza pandemic	18	6	11	3
Quality assessment§				
Low risk of bias in study design	24	12	14	4
Low risk of bias in patient groups excluded	20	8	14	4
Low risk of bias in case definition	10	9	9	4
Low risk of bias in sampling strategy	22	9	14	4
Low risk of bias in diagnostic test	23	11	12	3

* Data in the parenthesis were the numbers of imputed studies.
† LICs: low income countries; LMICs: lower-middle income countries; UMICs: upper-middle income countries; HICs: high income countries as per World Bank Classification.
‡ AFR: WHO African region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean region; EUR: WHO European region; SEAR: WHO South-East Asian region; WPR: WHO Western Pacific region.
§ As specified in the quality assessment criteria.

Table A18–1b. IFV – the number of included studies with hospitalisation rates and hCFRs (N=122)*

	IFV–ALRI (N=96)†	IFV–ALRI with hypoxaemia (N=17)	IFV–very severe ALRI (N=31)	hCFRs of IFV–ALRI (N=66)
Data by three narrow age groups‡	59	13§	24	28
New studies (not in the previous analysis)	45	13	24	28
From the collaboration network	30	13	22	27
Developing countries	45	11	18	23
World Bank income region**				
LICs	4	1	2	3
LMICs	16	8	8	7
UMICs	13	2	6	11
HICs	26	2	8	7
WHO region††				
AFR	14	5	6	11
AMR	14	4	7	9
EMR	1	0	0	0
EUR	8	1	4	3
SEAR	8	1	4	1
WPR	14	1	3	2
After the 2009 pandemic	30	9	18	23
Quality assessment: low risk of bias in ‡‡				
Study design	51	12	21	26
Adjustment for healthcare utilization	49	11	18	—
Patient groups excluded	53	10	18	22
Case definition	29	12	21	25
Sampling strategy	39	12	19	20
Diagnostic test	46	11	19	—

* This table shows the number of studies with data for three age groups - 0-5 m, 6-11 m, 12-59 m unless stated otherwise.
† The number is the number of all studies, regardless of age groups.
‡ 0-5 m, 6-11 m, 12-59 m.
§ The 13 studies with age-stratified data were from developing countries. For industrialised countries, the hospitalisations were estimated using data that not stratified by age in two studies.
** LICs: low income countries; LMICs: lower-middle income countries; UMICs: upper-middle income countries; HICs: high income countries as per World Bank Classification.
†† AFR: WHO African region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean region; EUR: WHO European region; SEAR: WHO South-East Asian region; WPR: WHO Western Pacific region.
‡‡ As specified in the quality assessment criteria.

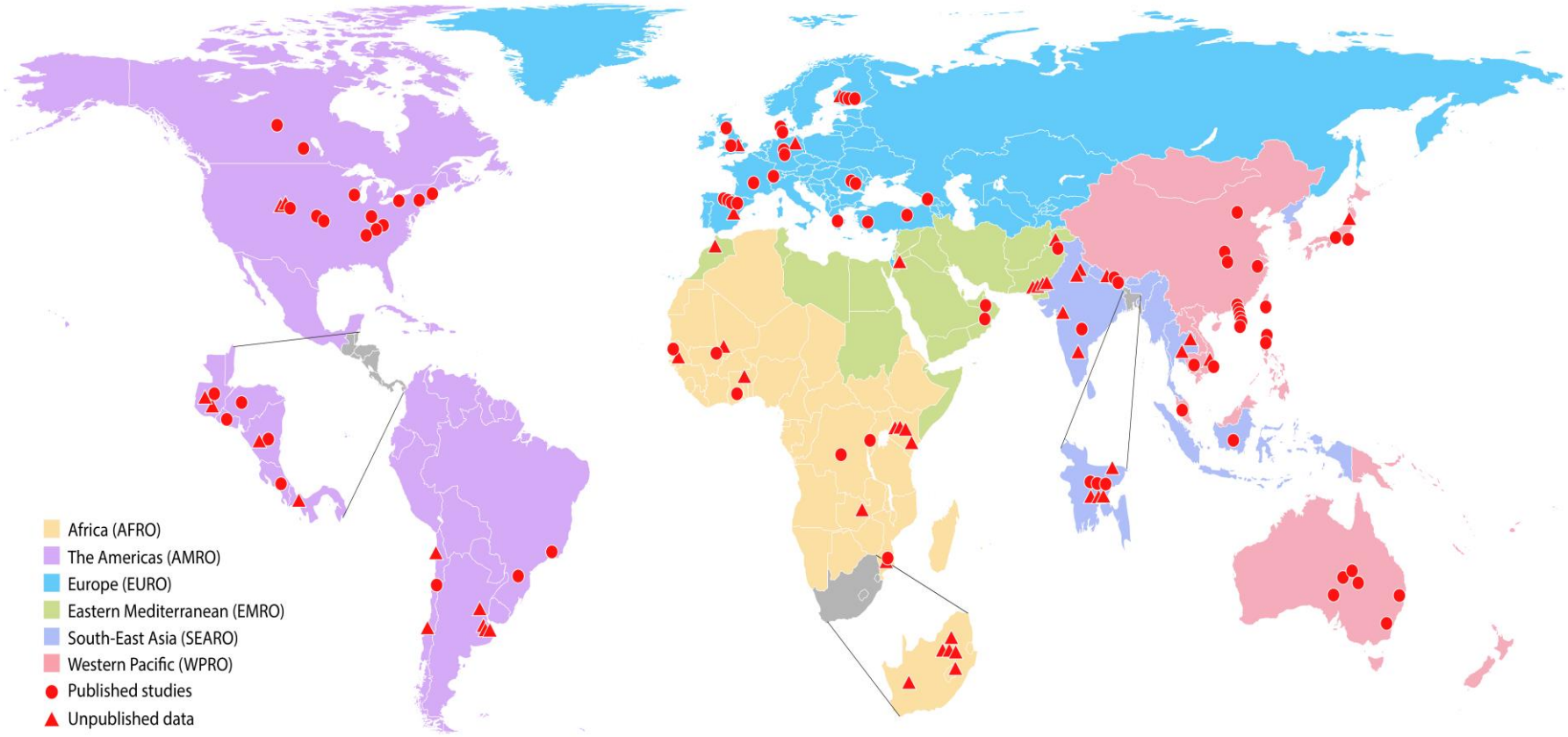

Figure A18–1. The location of included studies on IFV burden. This figure shows all studies with data on incidence rates, hospitalisation rates, and in–hospital case–fatality ratios for IFV.

Table A18–2a. hMPV – the number of studies by age, region, and period for each outcome.*

	Incidence rate (N=10)†	Hospitalisation rate (N=39)	Hospitalisation rate of hMPV–ALRI with hypoxaemia (N=21)	Proportion of hospitalised hMPV–ALRI (N=117)	hCFR (N=73)
From the collaboration network	5	18	21	41	33
0–59 m	9	38	18	78	57
Reporting by 0–5 m, 6–11 m, and 12–59 m	5	29	18	69	28
Developing countries	6	28	20	93	60
By World Bank income region					
LIC	1	3	2	5	5
LMIC	4	11	10	30	25
UMIC	2	11	6	51	24
HIC	4	14	3	31	19
By WHO region					
AFR	1	12	7	18	17
AMR	3	11	2	12	13
EMR	1	1	2	11	11
EUR	0	5	1	17	7
SEAR	3	7	3	13	8
WPR	2	3	6	46	17
By median study year					
By 2005	1	5	3	12	11
2006–2010	3	12	2	36	23
2011 onward	5	22	16	69	39
No of hMPV–ALRI cases					
0–99	9	24	NA	97	46
99–199	1	8	NA	15	10
200– ~	0	7	NA	5	10

Table A18–2b. hMPV– the number of studies that were included in the main analysis with a low risk of bias for each outcome. ‡

	Incidence rate (N=9)§	Hospitalisation rate (N=29)	Hospitalisation rate of hMPV–ALRI with hypoxaemia (N=18)	Proportion of hospitalised hMPV–ALRI (N=78)	hCFR (N=28)
Study design	9	28	18	70	27
Adjustment for healthcare utilization	NA	22	11	NA	NA
Patient groups excluded	5	20	13	61	21
Case definition	8	22	17	48	23
Sampling strategy	6	23	14	60	20
Test method	9	26	18	73	NA
Hypoxaemia ascertainment	NA	NA	8	NA	NA

* NA: not applicable.
† The number is the number of all studies, regardless of age groups.
‡ NA: not applicable.
§ The number refers to the number of studies included in the main analysis for each outcome. For incidence rates, all studies with data for 0–59 m were included. For hospitalisation rates and hCFRs, all studies with data for 0–5 m, 6–11 m, and 12–59 m were included.

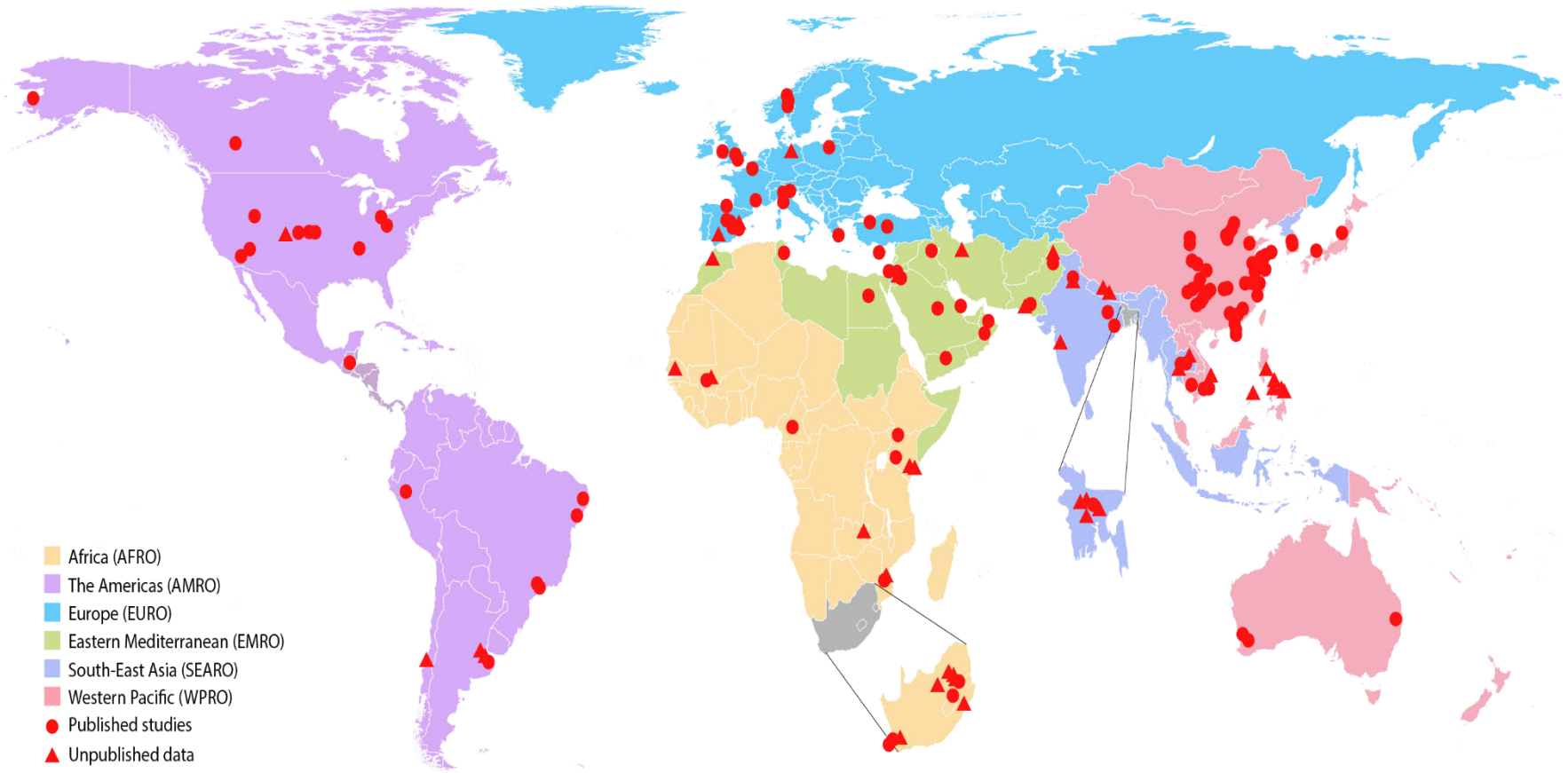

Figure A18–2. The location of included studies on hMPV burden. This figure shows all studies with data on incidence rates, hospitalisation rates, in–hospital case–fatality ratios, and proportions for hMPV.

Table A18–3a. hPIV– the number of studies by age, region, and period for each outcome.*

	Incidence rate (N=12)†	Hospitalisation rate (N=35)	Hospitalisation rate of hPIV–ALRI with hypoxaemia (N=14)	Proportion of hospitalised hPIV–ALRI (N=160)	hCFR (N=56)
From the collaboration network	5	19	14	37	30
0–59 m	11	33	13	91	46
Reporting data by 0–5 m, 6–11 m and 12–	5	26	13	77	27
Developing countries	7	26	14	136	51
By World Bank income region					
LICs	1	3	2	5	5
LMICs	5	10	6	26	22
UMICs	1	10	6	95	18
HICs	5	12	0	34	11
By WHO region					
AFR	1	10	5	17	16
AMR	2	9	2	19	10
EMR	1	1	2	16	7
EUR	1	4	0	15	3
SEAR	5	6	3	14	8
WPR	2	5	2	79	12
By median study year					
By 2005	3	7	1	34	8
2006–2010	2	11	2	42	15
2011 onward	5	17	11	84	32
No. of hPIV–ALRI cases					
0–99	9	22	NA	109	39
99–199	2	8	NA	25	10
200– ~	1	5	NA	26	7

Table A18–3b. hPIV– the number of studies that were included in the main analysis by risk of bias for each outcome.‡

	Incidence rate (N=11)§	Hospitalisation rate (N=26)	Hospitalisation rate of hPIV–ALRI with hypoxaemia	Proportion of hospitalised hPIV–ALRI (N=91)	hCFRs (N=27)
Study design	11	25	13	69	27
Adjustment for healthcare utilization	NA	17	6	NA	NA
Patient groups excluded	7	21	11	79	24
Case	9	19	12	51	25
Sampling	4	22	11	65	25
Test method	7	18	10	62	NA
Hypoxaemia ascertainment	NA	NA	10	NA	NA

* NA: not applicable.
† The number refers to the number of all studies identified in the review.
‡ NA: not applicable.
§ The number refers to the number of studies included in the main analysis for each outcome.

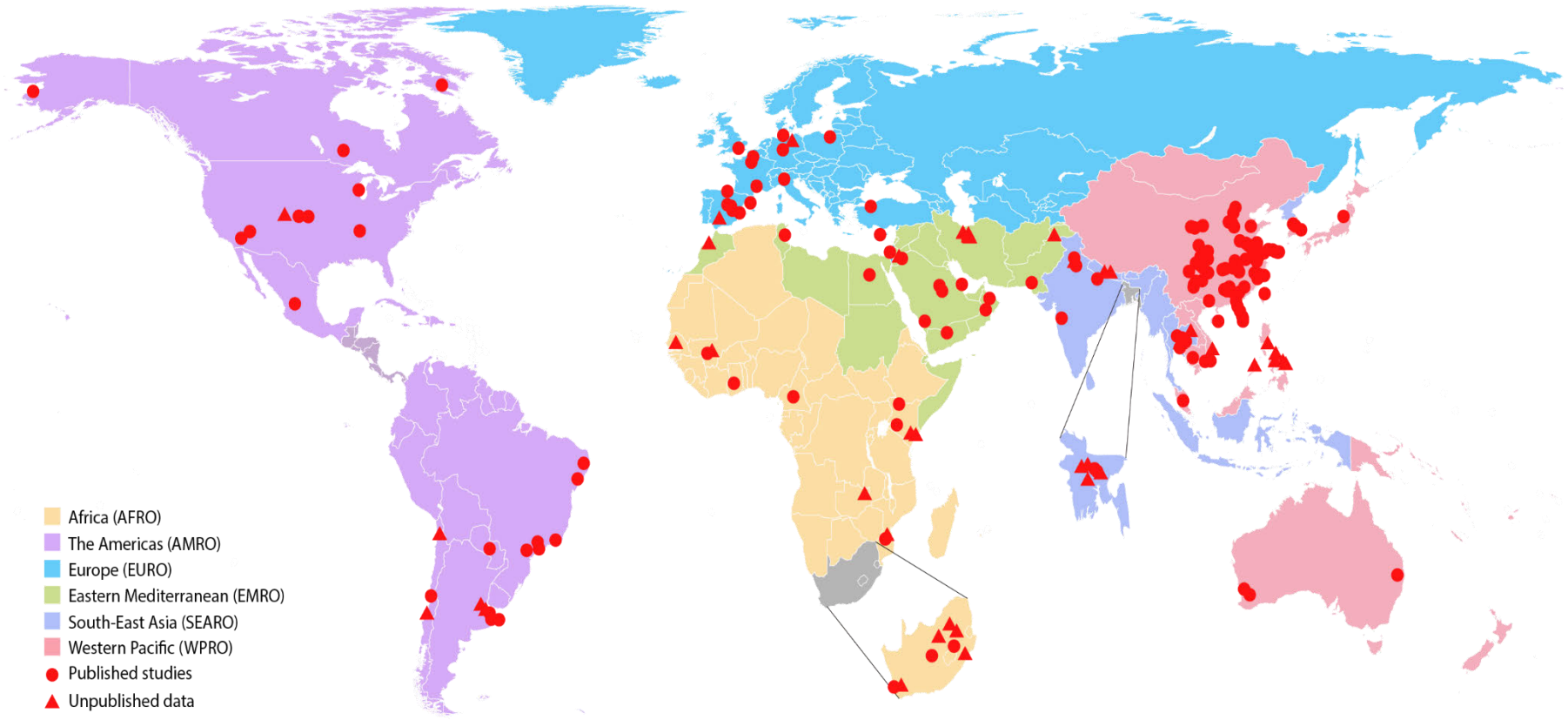

Figure A18 – 3. Location of hPIV studies (including studies on rates, proportions, and case–fatality ratios).

A19. Details of included studies

Table A19–1a. IFV – Description of studies reporting IFV–episodes incidence rates in children under five years (per 1,000 children per year).*†

Location (reference)	Case Definition	Denominator type	Specimen and diagnostic test	0–5 m	6–11 m	12–23 m	24–59 m	0–59 m
Bamako, Mali (Sep 2011–Jan 2014) (Tapia et al. 2016)	Fever; ARI AND Fever	Defined population base	NPS and OPS; PCR	83.1	--	--	--	--
IISP sites, USA (Oct 2009–Jul 2013) (Fowlkes et al. 2015)	ILI; ARI AND Fever	Census–derived estimate	NS, nasal aspirates, NPS, or OPS; PCR	--	--	--	13.2	9.7
Turku, Finland (Oct 2000–May 2002) (Heikkinen et al. 2004)	ARI AND Fever	Defined population base	NS; Viral culture and subsequent immunoperoxidase staining with monoclonal ant bodies	--	--	185.3	110.6	132.3
Senegal (Jan 2012–Dec 2013) (Diene Sarr et al. 2015)	Fever	Defined population base	NP and oral specimens; PCR	45.5	--	--	259.7	300.0
Senegal (Jan 2012–Dec 2013) (Diene Sarr et al. 2015)	Fever	Defined population base	NP and oral specimens; PCR	280	--	--	282.1	317.2
Nashville, TN, USA (Aug 1974–Jul 1999) (Neuzil et al. 2002)	ARI; Fever	Defined population base	NW; Culture and HI or DFA	--	--	114	81.7	95.0
Ballabhgarh, India (2001–2005) (Broor et al. 2007)	ARI	Defined population base	NPW; DFA	--	--	174.2	--	--
Kamalapur, Bangladesh (Apr 2004–Dec 2007) (Brooks et al. 2010)	ARI AND Fever	Defined population base	NPW; Viral culture and HI	--	--	78.7	71.5	92.7
Managua, Nicaragua (Sep 2012–Sep 2015) (Gordon and colleagues, unpublished)	ARI; Fever	Defined population base	NS and TS; PCR	102.9	244.0	263	--	--
Kamalapur, Bangladesh (2008–2015) (Brooks and colleagues, unpublished)	ARI AND Fever	Defined population base	NPW; PCR and tissue culture	9.3	110.6	199.5	274.4	126.7
Nepal (April 2011–May 2014) (Omer and colleagues, unpublished)	ARI AND Fever	Defined population base	NPS; PCR	94.1	--	--	--	--
Mali (Sep 2011–Jan 2014) (Omer and colleagues, unpublished)	ARI AND Fever; Fever	Defined population base	NPS; PCR	35.5	--	--	--	--

* NPA: nasopharyngeal aspirate. NPS: nasopharyngeal swab. NPW: nasopharyngeal wash. OPS: oropharyngeal swab. NW: nasal wash. NS: nasal swab. TS: throat swab. PCR: polymerase chain reaction. IFA: indirect immunofluorescence assay. DFA: direct immunofluorescence assay. ELISA: enzyme-linked immunosorbent assay. HI: hemagglutination-inhibition assay. RIDT: rapid influenza diagnostic test. SPIA: solid-phase immunoassay. MN: micro-neutralization assay. TRFIA: time-resolved fluoroimmunoassay. ILI: influenza like illness (fever and either cough or sour throat). ARI: any of respiratory symptoms, including cough, sour throat, rhinitis, pharyngitis, and others.

† Incidence rates were adjusted for the proportion of testing in eligible patients where available.

Location (reference)	Case Definition	Denominator type	Specimen and diagnostic test	0–5 m	6–11 m	12–23 m	24–59 m	0–59 m
South Africa (Mar 2011–May 2013) (Omer and colleagues, unpublished)	ARI; Fever	Defined population base	NPS; PCR	86.6	--	--	--	--
Nam, Vietnam (2007–2010) (Horby et al. 2012)	ILI	Defined population base	NS and TS; PCR	--	--	--	--	27.8
Izu–Oshima Island, Japan (Jan 2009–Mar 2011) (Inamasu et al. 2012)	ILI	Census–derived estimate	NPS; RIDT and PCR	--	--	--	--	180.4
Japan (Dec–Jun, 2004–2008) (Kimura et al. 2011)	ILI	Census–based estimate	NPS or NPA; Rapid antigen test kit	--	--	--	--	124.1
Berne, Switzerland (Apr 1999–Dec 2004) (Regamey et al. 2008)	ARI	Defined population base	NS; PCR	--	--	--	--	--
India (Aug 2012–Dec 2014) (Kumar et al. 2017)	ARI; Fever	Defined population base	NPA; PCR	--	--	--	--	--
Southwest Finland (Jan 2010–Apr 2012) (Teros-Jaakkola et al. 2017)	ARI; Fever	Defined population base	NS; PCR	--	--	--	--	--
USA (Jul 2010–Jun 2014) (Buck et al. 2017)	ARI	Defined population base	NA; NA	--	--	--	--	--
Sydney, Australia (May–Nov 2011) (J. P. Li-Kim-Moy et al. 2017)	ARI AND Fever	Defined population base	NS and TS; PCR	--	--	--	--	--
Nepal (Apr 2011–Apr 2013) (Steinhoff et al. 2017)	ARI; Fever	Defined population base	NS; PCR	181.3	--	--	--	--
Australia (2010–2014) (Sarna et al. 2018)	ARI	Defined population base	NS; PCR	--	--	--	--	--
Romania (2011–2016) (Gefenaite et al. 2018)	ILI	Census–derived estimate	NPS; PCR	--	--	--	--	1.4
Nepal (2011–2013) (Katz et al. 2018)	ARI/Fever	Defined population base	NS; PCR	190.5	--	--	--	--
Spain (2010–2016) (Oliva et al. 2018)	ILI	Census derived estimates	Respiratory swab; --	--	--	--	--	24.4
Japan (2004–2008) (Kimura et al. 2011)	ILI	Census derived estimates	NPS or NPA; Rapid antigen test	--	--	--	--	124.1

Table A19–1b. IFV – Description of studies reporting IFV–ALRI incidence rates in children under five years (per 1,000 children per year) *†

Location (reference)	Case Definition	Denominator type	Specimen and diagnostic test	0–5 m	6–11 m	12–23 m	24–59 m	0–59 m
Multicentre, Germany (Nov 1999– Oct 2001) (Forster et al. 2004)	ALRI; Croup	Census–derived estimate	NPA; PCR	--	--	12.4	--	--
Nashville, TN, USA (Aug 1974–Jul 1999) (Neuzil et al. 2002)	ALRI	Defined population base	NW; Culture and HI or DFA	--	--	10.5	3.9	8.5
Ballabhgarh, India; rural (2001–2005) (Broor et al. 2007)	ALRI	Defined population base	NPW; DFA	--	--	58.1	--	--
Kamalapur, Bangladesh; urban (Apr 2004 – Dec 2007) (Brooks et al. 2010)	ALRI	Defined population base	NPW; Culture and HI	--	--	70.6	20.3	25.4
Faridabad, Haryana, India; rural (Aug 2012–Aug 2014) (Krishnan and colleagues, unpublished)	ALRI	Census–derived estimate	OP or nasal specimens; PCR	18.0	19.0	21.7	5.4	10.9
Managua, Nicaragua (Sep 2012–Sep 2015) (Gordon and colleagues, unpublished)	ALRI	Defined population base	NS and TS; PCR	5.9	32.2	17.3	--	--
Kamalapur, Bangladesh; urban (2008–2014) (Brooks and colleagues, unpublished)	ALRI AND No wheeze	Defined population base	NPW; PCR and tissue culture	3.4	29.4	40.0	20.2	17.9
Oshikhandass, Pakistan; rural (Apr 2012–Mar 2014) (Rasmussen and colleagues, unpublished)	ALRI	Defined population base	NPS; PCR	0	0	17.4	3.8	5.8
Western Province, South Africa (Mar 2012–Dec 2016) (Zar and colleagues, unpublished)	ALRI	Census–derived estimate	NPS; PCR	50.4	24.1	21.3	1.2	22.8
Turku, Finland (Oct 2000–May 2002) (Heikkinen et al. 2004)	ALRI	Defined population base	NS; Culture and subsequent immunoperoxidase staining with monoclonal ant bodies	--	--	--	--	--
India (Aug 2012–Dec 2014) (Kumar et al. 2017)	ALRI	Defined population base	NPA; PCR	--	--	--	--	--
Brisbane, Australia (2010–2014) (Sarna et al. 2018)	ALRI; wheeze	Defined population base	NS; PCR	--	--	--	--	--

* NPA: nasopharyngeal aspirate. NPS: nasopharyngeal swab. NPW: nasopharyngeal wash. OPS: oropharyngeal swab. NW: nasal wash. NS: nasal swab. TS: throat swab. PCR: polymerase chain reaction. IFA: indirect immunofluorescence assay. DFA: direct fluorescent antibody. ELISA: enzyme-linked immunosorbent assay. HI: hemagglutination-inhibition assay. RIDT: rapid antigen detection test. SPIA: solid-phase immunoassay. MN: micro-neutralization assay. TRFIA: time-resolved fluoroimmunoassay. ARI: any of respiratory symptoms, including cough, sour throat, rhinitis, pharyngitis, and others. ALRI, sALRI, and vsALRI: WHO definition for ALRI, chest wall indrawing ALRI, and very severe ALRI.

† Incidence rates were adjusted for the proportion of testing in eligible patients where available.

Table A19–1c. IFV – Description of studies reporting incidence rates of IFV–severe ALRI in children under five years (per 1,000 children per year)*†

Location (reference)	Case Definition	Denominator type	Specimen and diagnostic test	0–5 m	6–11 m	12–23 m	24–59 m	0–59 m
Kamalapur, Bangladesh (Apr 2004–Dec 2007) (Brooks et al. 2010)	sALRI	Defined population base	NPW; Viral culture and HI	--	--	1.7	0	0.6
Haryana, India (Aug 2012–Aug 2014) (Krishnan and colleagues, unpublished)	sALRI	Census–derived estimate	OP or nasal specimens; PCR	13.5	6.3	6.2	1.6	4.0
Managua, Nicaragua (Sep 2012–Sep 2015) (Gordon and colleagues, unpublished)	sALRI	Defined population base	NS and TS; PCR	0	10.7	4.7	--	--
Kamalapur, Bangladesh (2008–2014) (Brooks and colleagues, unpublished)	sALRI	Defined population base	NPW; PCR and tissue culture	0.3	1.7	1.4	0.6	0.7
Sindh, Pakistan (Oct 2011–June 2014) (Ali and colleagues, unpublished)	sALRI	Defined population base	NPS; PCR	7.8	--	--	--	--
Western Province, South Africa (March 2012–Dec 2016) (Zar and colleagues, unpublished)	sALRI	Census–derived estimate	NPS; PCR	43.5	18.1	14.6	0	17.6
Mirzapur, Bangladesh (Oct 1993–Aug 1996) (Hasan et al. 2014)	sALRI	Defined population base	NPA; ELISA	--	--	--	--	--
Sylhet, Bangladesh (2011–2013) (Saha and colleagues, unpublished)	pSBI	Defined population estimate	NPS or OPS; PCR	--	--	--	--	--
Karachi, Pakistan (2012–2013) (Saha and colleagues, unpublished)	pSBI	Defined population estimate	NPS or OPS; PCR	--	--	--	--	--
Matiari, Pakistan (2012–2013) (Saha and colleagues, unpublished)	pSBI	Defined population estimate	NPS or OPS; PCR	--	--	--	--	--
Vellore, India (2013–2014) (Saha and colleagues, unpublished)	pSBI	Defined population estimate	NPS or OPS; PCR	--	--	--	--	--
Odisha, India (2013–2014) (Saha and colleagues, unpublished)	pSBI	Defined population estimate	NPS or OPS; PCR	--	--	--	--	--
Nepal (Apr 2011–May 2014) (Omer and colleagues, unpublished)	sALRI	Defined population base	NPS; PCR	6.6	--	--	--	--
Mali (Sep 2011–Jan 2014) (Omer and colleagues, unpublished)	sALRI	Defined population base	NPS; PCR	0	--	--	--	--

* NPA: nasopharyngeal aspirate. NPS: nasopharyngeal swab. NPW: nasopharyngeal wash. OPS: oropharyngeal swab. NS: nasal swab. TS: throat swab. PCR: polymerase chain reaction. IFA: indirect immunofluorescence assay. DFA: direct fluorescent antibody. ELISA: enzyme-linked immunosorbent assay. HI: hemagglutination-inhibition assay. RIDT: rapid influenza diagnostic test. SPIA: solid-phase immunoassay. MN: micro-neutralization assay. TRFIA: time-resolved fluoroimmunoassay. ALRI, sALRI, and vsALRI: WHO definition for ALRI, chest wall indrawing ALRI, and very severe ALRI applied by a health worker. pSBI: WHO possible severe bacterial infections.

† Incidence rates were adjusted for the proportion of testing in eligible patients where available.

Table A19–1d. IFV – Description of studies reporting incidence rates of IFV–very severe ALRI in children under five years (per 1,000 children per year) *†

Location (reference)	Case Definition	Denominator type	Specimen and diagnostic test	0–5 m	6–11 m	12–23 m	24–59 m	0–59 m
Haryana, India (Aug 2012–Aug 2014) (Krishnan and colleagues, unpublished)	vsALRI	Census–derived estimate	OP and nasal specimens; PCR	13.5	3.2	3.1	0.5	2.3
Managua, Nicaragua (Sep 2012–Sep 2015) (Gordon and colleagues, unpublished)	vsALRI	Defined population base	NS and TS; PCR	0	2.7	1.6	..	..
Kamalapur, Bangladesh (2007–2014) (Brooks and colleagues, unpublished)	vsALRI	Defined population base	NPW; PCR and tissue culture	0	0.2	0.2	0	0.1
Western Province, South Africa (Mar 2012–Dec 2016) (Zar and colleagues, unpublished)	vsALRI	Census–derived estimate	NPS; PCR	1.7	2.0	3.4	0	1.9

* NPA: nasopharyngeal aspirate. NPS: nasopharyngeal swab. NPW: nasopharyngeal wash. OPS: oropharyngeal swab. NS: nasal swab. TS: throat swab. PCR: polymerase chain reaction. ALRI, sALRI, and vsALRI: WHO definition for ALRI, chest wall indrawing ALRI, and very severe ALRI applied by a health worker.

† Incidence rates were adjusted for the proportion of testing in eligible patients where available.

Table A19–1e. IFV – Description of studies reporting IFV–ALRI hospitalisation rates in children under five years (per 1,000 children per year) *†

Location (reference)	Case Definition	Denominator type	Specimen and diagnostic test	0–5 m	6–11 m	12–23 m	24–59 m	0–59 m
Baguio City, Philippines; urban (2009–2011) (Tallo et al. 2014)	ALRI	Census–derived estimate	OPS or NPS; PCR	4.4	--	--	2.4	3.9
Jingzhou, China; urban (Apr 2010–Mar 2012) (Yu et al. 2014)	ARI AND Fever	Census–derived estimate	NPS; PCR	25.1	37	23.6	21.4	21.9
Multistate, USA (Oct 2003–Apr 2012) (Chaves et al. 2014)	Flu	Census–derived estimate	NPS or OPS; PCR, culture, DFA, IDFA, or RIDT	2	0.9	--	--	--
Hong Kong (2004–2011)(Chiu et al. 2014)	ARI AND Fever	Census–derived estimate	NPA; DFA and viral culture, PCR	8.4	7.6	7.8	9.7	9.0
Hong Kong (Apr 2005–Mar 2011)(Nelson et al. 2014)	All	Defined population base	NPA; Viral culture and IF	12.8	13.5	11.8	9.0	10.3
Bondo district, Kenya (Jun 2007–May 2009) (Nair et al. 2011)	ALRI	Census–derived estimate	NPS or OPS; PCR	--	--	1.3	0.3	--
Multicentric, Germany (Nov 1999– Oct 2001) (Forster et al. 2004)	ARI	Census–derived estimate	NPA; PCR	--	--	1.4	--	--
Multistate, USA (Oct–April 2003–2008) (Dawood et al. 2010)	Flu	Census–derived estimate	NPS or OPS; PCR, culture, DFA/IDFA, or RIDT	--	--	0.5	0.2	0.4
Kiel, Germany (Jul 1996–Jun 2000) (Weigl et al. 2005)	ARI	Census–derived estimate	NPA; RT–PCR	--	--	--	--	1.2
Gipuzoka, Spain (Jul 2001–Jun 2004) (Montes et al. 2005)	ARI	Census–derived estimate	NPA; Viral culture and PCR	4.1	0.8	0.7	0.5	0.9
East London, United Kingdom (Oct 2002– Sep 2004) (Ajayi-Obe et al. 2008)	ARI	Census–derived estimate	NPA; IFA and PCR	4.3	--	--	0.7	1.6
Leicester, United Kingdom (Oct 2001– Jun 2002) (Nicholson et al. 2006)	ARI	NHS data base	NS and TS; PCR	--	--	2.0	--	1.6

* NPA: nasopharyngeal aspirate. NPS: nasopharyngeal swab. NPW: nasopharyngeal wash. OPS: oropharyngeal swab. NS: nasal swab. TS: throat swab. NW: nasal wash. BAL: bronchoalveolar lavage. ETA: endotracheal aspirate. PCR: polymerase chain reaction. IFA: indirect immunofluorescence assay. DFA: direct fluorescent antibody. ELISA: enzyme-linked immunosorbent assay. IF: immunofluorescence. HI: hemagglutination-inhibition assay. RIDT: rapid influenza diagnostic test. SPIA: Solid-phase immunoassay. EIA: enzyme immunoassay. MN: micro-neutralization assay. TRFIA: time-resolved fluoroimmunoassay. ARI: any respiratory infections/symptoms (acute one of cough, sore throat, shortness of breath, coryza); ICD-codes for influenza & pneumonia (excluding non-respiratory manifestations), or acute infections (fever or <35 degree C) with any respiratory signs. ALRI: physician-diagnosed pneumonia and/or bronchiolitis, or WHO definition for ALRI requiring hospitalisation. All: all diagnosis related to influenza (including influenza & pneumonia and other non-respiratory illnesses). Flu: evidence of a positive influenza test.

† Hospitalisation rates were adjusted for the proportion of testing in hospitalised ALRI patients where available.

Location (reference)	Case Definition	Denominator type	Specimen and diagnostic test	0–5 m	6–11 m	12–23 m	24–59 m	0–59 m
Nha Trang, Vietnam (Mar 2007– Feb 2008) (Yoshida et al. 2010)	ARI	Census–derived estimate	NPA; PCR	--	--	18.4	4.2	8.7
Hong Kong (Jul 1997– Jun 1999) (Nelson et al. 2007)	ARI	Census–derived estimate	NPA; Viral culture and serology	--	--	4.4	2.2	3
Hong Kong (Oct 2003– Sep 2006) (Chiu et al. 2009)	ARI AND Fever	Census–derived estimate	NPA; DFA and viral culture	--	--	7.3	7.2	7.2
Suzhou, China (Jan 2007– Dec 2008) (Ji et al. 2010)	ALRI	Census–derived estimate	NPA; DFA	--	--	0.1	0.2	0.2
Nashville, Rochester; Cincinati, USA (Oct 2001–Sep 2004) (Poehling et al. 2006)	ARI; Fever	Census–derived estimate	NS and TS; Viral Culture and PCR	4.5	--	--	0.3	1
Monroe County NY, and Davidson County TN, USA (Oct 2000 – Sep 2001) (Iwane et al. 2004)	ARI	Census–derived estimate	NS and TS; Viral Culture and PCR	2.4	1	0.5	0.2	0.6
Salt Lake County, Utah, USA (Jul 2001–Jun 2004) (Ampofo et al. 2006)	ARI	Census–derived estimate	NPA; DFA	7.4	3.3	2.9	1	2.6
Philadelphia, USA (Jul 2000– Jun 2004) (Coffin et al. 2007)	All	Census–derived estimate	Nasal aspirates; SPIA, DFA and viral culture	--	--	--	0.7	2.1
Davidson County, USA (2003–2004)(Grijalva et al. 2006)	ARI; Fever	Census–derived estimate	NS and TS; Viral culture, PCR, RIDT, IFA, serology	5.4	--	--	0.3	1.2
Soma and Shinchi, Japan (2002–2008)(Nair et al. 2011)	ARI AND Fever	Defined population base	NS; RIDT	--	33.7	37.3	24.3	--
Nashville, TN, USA (Aug 1974–Jul 1999) (Neuzil et al. 2002)	ARI; Fever	Defined population base	NW; Culture and HI or DFA	--	--	3.5	0	2.3
Manhiça, Mozambique (Sep 2006–Sep 2007) (Nair et al. 2011)	ALRI	Defined population base	NPA; PCR	4.5	3	3.4	0.3	1.7
Baguio City, Philippines (Jan 2012–Dec 2014) (Kamigaki et al. 2017)	ALRI	Census derived estimate	OPS or NPS; PCR	8.7	--	--	3.6	7.2
Australia (2006–2015) (Li-Kim-Moy et al. 2016)	ARI	Census derived estimate	--; --	1.9	--	--	0.4	0.8
Memphis, Nashville, and Salt Lake City; urban (Jan 2010–Jun 2012)(Jain et al. 2015)	ALRI	Census–derived estimate	NPS and OPS; PCR, serology	--	--	--	0.1	0.2
Athens, Greece (2002–2003; 2004–2005) (Sakkou et al. 2011)	ARI; Fever	Census–derived estimate	NPA; PCR	--	--	--	--	--
Turku, Finland; (Jul 1988–Jun 2004)(Silvennoinen et al. 2011)	All	Defined population base	NPA; IFA and RIDT	2.8	--	--	--	--
St. Elizabeth, Lwak, Asembo, Kenya; rural (2010–2014) (Chaves and colleagues, unpublished)	ALRI	Census–derived estimate	NPS and OPS; PCR	0	13.1	7.2	0.9	3.3

Location (reference)	Case Definition	Denominator type	Specimen and diagnostic test	0–5 m	6–11 m	12–23 m	24–59 m	0–59 m
Siaya County, Kenya; rural (2010–2014) (Chaves and colleagues, unpublished)	ALRI	Census–derived estimate	NPS and OPS; PCR	1.8	2.1	1.9	0.6	1.1
Soweto, Gauteng, South Africa; urban (Mar 1998 to Oct 2005) (Madhi and colleagues, unpublished)	ALRI	Defined population base	NPA; IFA	4	2.1	1.8	0.3	1.1
Amman, Jordan; urban (Mar 2010–Mar 2013) (Khuri–Bulos and colleagues, unpublished)	ALRI	Census–derived estimate	NS and TS; PCR	..	..	0.2	..	..
Manhiça, Mozambique; rural (Jan 2011–June 2014) (Bassat and colleagues, unpublished)	ALRI	Census–derived estimate	NPA; PCR	1.1	1.5	0.6	0.2	0.5
Kilifi, Kenya; rural and semi–urban (Jan 2007–Dec 2016) (Nokes and colleagues, unpublished)	ALRI	Census–derived estimate	NPS; PCR	1.7	1.8	1.0	0.4	0.8
Muang District, Nakhon Phanom Province, Thailand (PERCH); rural (2012–2013) (O'Brien and colleagues, unpublished)	ALRI	Census–derived estimate	NP/OP and induced sputum; PCR	..	..	0	0.1	0.1
Muang District, Sa Kaeo Province, Thailand; rural (2012–2013) (O'Brien and colleagues, unpublished)	ALRI	Census–derived estimate	NP/OP and induced sputum; PCR	..	..	0.4	0.2	0.2
Nha Trang city, Vietnam; urban and sub–urban (2008–2013) (Yoshida and colleagues, unpublished)	ALRI	Census–derived estimate	NP specimens; PCR	..	..	1.4	0.2	0.7
Basse, Upper River Region, The Gambia (PERCH); rural (Nov 2011–Nov 2013) (O'Brien and colleagues, unpublished)	ALRI	Census–derived estimate	NPS, OPS, induced sputum; PCR	3.3	0.6	0.2	0.3	0.6
Bersheba, Israel (Sep–Mar 2011–2016) (Katz and colleagues, unpublished)	ARI; Fever	Medical Records	OPS and NS; PCR	11.5	12.6	6	3.5	5.3
Nakhon Phanom and Sa Kaeo Provinces, Thailand; rural (Jan 2005–Dec 2011) (Thamtithiwat and colleagues, unpublished)	ARI	Census–derived estimate	NPS; PCR	2.9	9.1	9	4.4	5.6
Pune district, India; rural (May 2009–Apr 2013) (Hirve and colleagues, unpublished)	ALRI	Census–derived estimate	NPS; PCR	0	1.2	0	0.1	0.2
Kamalapur, Bangladesh (2007–2014) (Brooks and colleagues, unpublished)	ALRI	Defined population base	NPW; PCR and tissue culture	0.2	0.8	2.5	0.4	0.7
David City, Panama (2014–2016) (Jara and colleagues, unpublished)	ALRI	Census–derived estimate	NPS or OPS; PCR	..	..	8.6	1.2	4.9
Ciudad de Buenos Aires, Argentina; urban (Jun 2008–Dec 2010) (Echavarria and colleagues, unpublished)	ALRI	Defined population base	NPA; IFA	..	..	4.4	0.6	4

Location (reference)	Case Definition	Denominator type	Specimen and diagnostic test	0–5 m	6–11 m	12–23 m	24–59 m	0–59 m
Turku, Finland; urban (Jan 2010–Jun 2012) (Heikkinen and colleagues, unpublished)	ALRI	Census–derived estimate	NS; TRFIA	2	0.7	0.7	0.1	0.5
Aurora, Colorado, USA; urban (Jan 2011–Oct 2015) (Simões and colleagues, unpublished)	ALRI	Census–derived estimate	--; --	--	--	0.5	0.2	0.3
Paarl, Western Province, South Africa (Jun 2012–Dec 2016) (Zar and colleagues, unpublished)	ALRI	Defined population base	NPS; PCR	17.1	7.9	1.1	1.1	5.6
Region VI Buenos Aires Province, Argentina; urban /slums/semi–rural (2011–2013) (Polack and colleagues, unpublished)	ALRI	Census–derived estimate	NPA; PCR	2.9	2.1	1.4	--	--
Quetzaltnango, Guatemala (2010–2016) (McCracken and colleagues, unpublished)	ALRI	Census–derived estimate	NPS and OPS; PCR	1.6	0.9	0.6	0.1	0.5
Santa Rosa, Guatemala (2010–2016) (McCracken and colleagues, unpublished)	ALRI	Census–derived estimate	NPS and OPS; PCR	2.1	0.7	1.3	0.1	0.6
Tagbilaran, Bohol, Philipines; Dauis, Baclayon, Panglao, Cortes, Balilihan, Bohol, Philippines; mixed urban–rural (July 2000–Dec 2004) (Lucero and colleagues, unpublished)	ALRI	Defined population base	NPA; Viral culture	2.4	3.0	1.3	--	--
Valencia Region, Spain (2014–2017) (Mira Iglesias and colleagues, unpublished)	All	Census–derived estimate	NPS and NS; PCR	--	--	1.3	0.3	0.9
Buenos Aires, Argentina; urban (2009–2016) (Gentile and colleagues, unpublished)	ALRI	Census–derived estimate	NPA; PCR	--	--	3.4	1.1	2.6
Soweto, Gauteng, South Africa (2015–2017) (Madhi and colleagues, unpublished)	ALRI	Census–derived estimate	NPS; PCR	--	--	1.8	0.4	2.3
Klerksdorp, North West Province, South Africa; peri–urban (2013–2015) (Cohen and colleagues, unpublished)	ALRI; Sepsis	Census–derived estimate	NPA; PCR	1.3	1.8	1.4	0.3	0.8
Pietermaritzburg, Kwa–Zulu Natal Province, South Africa; peri–urban (2013–2015) (Cohen and colleagues, unpublished)	ALRI; Sepsis	Census–derived estimate	NPA; PCR	1.3	2.0	0.7	0.1	0.5
Soweto, Gauteng, South Africa; urban (2009–2012) (Cohen and colleagues, unpublished)	ALRI; Sepsis	Census–derived estimate	NPA; PCR	1.6	1.4	0.7	0.1	0.5
Concepcion, Chile; mixed urban/rural (2012–2013) (Fasce and colleagues, unpublished)	ALRI	Census–derived estimate	NPA or NPS; PCR	--	--	0.4	0.2	0.4
Iquique, Chile; mixed urban–rural (2012–2013) (Fasce and colleagues, unpublished)	ALRI	Census–derived estimate	NPA; PCR	--	--	0.4	0.4	0.7
New Haven County, CT, USA (Oct 2003–April 2010) (Yousey-Hindes and Hadler 2011)	Flu	Census–derived estimate	NPS or OPS; Viral culture, DFA or IDFA, PCR, and RIDT	--	--	--	--	1

Location (reference)	Case Definition	Denominator type	Specimen and diagnostic test	0–5 m	6–11 m	12–23 m	24–59 m	0–59 m
Kishoreganj, Bogra, Comilla and Barisal, Bangladesh (2010–2014) (Homaira et al. 2016)	ARI	Census–derived estimate	NS and TS; PCR	--	--	--	--	0.4
Sohar, Oman (2008–2013) (Al-Awaidy et al. 2015)	ALRI	Census–derived estimate	OPS and NPS; PCR	--	--	--	--	0.3
Ibra, Oman (2008–2013)(Al-Awaidy et al. 2015)	ARI	Census–derived estimate	OPS and NPS; PCR	--	--	--	--	0.4
SQH, Oman (2008–2013) (Al-Awaidy et al. 2015)	ARI	Census–derived estimate	OPS and NPS; PCR	--	--	--	--	0.4
El Salvador (2009–2012)(Descalzo et al. 2016)	All	Census–derived estimate	Nasal and pharyngeal specimens; PCR and IFA	--	--	--	--	1.8
Guatemala (2009–2012) (Descalzo et al. 2016)	All	Census–derived estimate	Nasal and pharyngeal specimens; PCR and IFA	--	--	--	--	0.7
Honduras (2009–2012) (Descalzo et al. 2016)	All	Census–derived estimate	Nasal and pharyngeal specimens; PCR and IFA	--	--	--	--	0.9
Nicaragua (2009–2012) (Descalzo et al. 2016)	All	Census–derived estimate	Nasal and pharyngeal specimens; PCR and IFA	--	--	--	--	4.5
Madrid, Spain (1997–2003)(Rojo et al. 2006)	ARI; Fever	Census–derived estimate	Nasal or throat aspirates; Viral culture and subsequent fluorescent staining	--	--	--	--	--
South Australia, Australia (1996–2006) (D'Onise and Raupach 2008)	ARI	Census–derived estimate	--; Viral Culture, PCR	--	--	--	--	0.6
Milwaukee, Wisconsin, USA (Nov 1996– Oct 1998) (Henrickson et al. 2004)	ARI; Fever	Census–derived estimate	NPS, BAL, TS, ETA; PCR, Tissue culture, EIA	--	--	--	--	1.5
Rio de Janeiro, Brazil (1987–1989) (Sutmoller et al. 1995)	ALRI	Defined population base	NPA; IFA, viral culture	--	--	--	--	2.5
Santa Rosa, Guatemala (2008) (Nair et al. 2011)	ARI	Census–derived estimate	NPS or OPS; PCR	--	--	--	--	0.7
Ghana (May 2013–April 2015) (Ntiri et al. 2016)	ARI AND Fever	Census derived estimate	NPS, OPS; PCR	--	--	--	--	3
England, United Kingdom (2010–2015)(Boddington et al. 2017)	ARI AND Fever	Census derived estimate	--; PCR	--	--	--	--	0.3
Germany (Jan 2005–Dec 2012) (Von Der Beck et al. 2017)	ARI	Census derived estimate	--; --	--	--	--	--	0.3

Location (reference)	Case Definition	Denominator type	Specimen and diagnostic test	0–5 m	6–11 m	12–23 m	24–59 m	0–59 m
Hamilton County, Ohio (Cincinnati); Monroe County, New York (Rochester); and Davidson County, Tennessee (Nashville) (2004–2009) (Poehling et al. 2013)	ARI; Fever	Census–derived estimate	NS and TS; PCR	--	--	--	--	0.6
Scotland, United Kingdom (Nov 2012–Apr 2013) (Harvala et al. 2014)	ALRI	Census–derived estimate	NS and TS; PCR	--	--	--	--	2.8
Leganes, Madrid, Spain (Oct 2011–Dec 2012)(Olabarrieta et al. 2015)	ARI	Defined population base	NPA; PCR	--	--	--	--	--
Multistate, USA (Oct 2010–Apr 2011) (Chaves et al. 2013)	Flu	Census–derived estimate	NPS or OPS; Culture, DFA, IFA, RIDT, or PCR	--	--	--	--	0.5
Tone and Cinkasse districts, Togo; mixed urban–rural (August 2011–Oct 2013 and Aug 2014–July 2015) (Moïsi and colleagues, unpublished)	ALRI	Census–derived estimate	NPA; PCR	--	--	--	--	0.1
Soweto, South Africa (March 2011–May 2013) (Omer and colleagues, unpublished)	ALRI	Defined population base	NPS, PCR	3.9	--	--	--	--
Kinshasa Province, Congo, Dem. Rep (2013–2015) (Babakazo et al. 2018)	ALRI	Census–derived estimate	OPS and NPS; PCR	--	--	--	--	2.3
Svay Rieng, Cambodia (2015) (Ieng et al. 2018)	ALRI–Fever	Census–derived estimate	NPS; PCR	--	--	--	--	0.1
Siem Reap, Cambodia (2016) (Ieng et al. 2018)	ALRI–Fever	Census–derived estimate	NPS; PCR	--	--	--	--	2.6
Kampong Cham, Cambodia (2016) (Ieng et al. 2018)	ALRI–Fever	Census–derived estimate	NPS; PCR	--	--	--	--	3.9
Rwanda (2012–2014) (Nyamusore et al. 2018)	ARI–Fever	Census–derived estimate	NPS and OPS; PCR	--	--	--	--	1.7
Spain (2010–2016) (Oliva et al. 2018)	ALRI	Census–derived estimate	Respiratory swab; --	--	--	--	--	0.2
Chile (2012–2014) (Sotomayor et al. 2018)	ARI–Fever	Census–derived estimate	NPA and NPS; PCR and IF	--	--	--	--	0.7
Deli Serdang, Indonesia (2013–2016) (Susilarini et al. 2018)	ARI–Fever	Census–derived estimate	Respiratory specimen; PCR	--	--	--	--	1.5
Balikpapan, Indonesia (2013–2016) (Susilarini et al. 2018)	ARI–Fever	Census–derived estimate	Respiratory specimen; PCR	--	--	--	--	6.1
Gunung Kidul, Indonesia (2013–2016) (Susilarini et al. 2018)	ARI–Fever	Census–derived estimate	Respiratory specimen; PCR	--	--	--	--	2.5
Beijing, China (2014–2016) (Yi et al. 2018)	ARI–Fever	Census–derived estimate	TS; PCR	--	--	--	--	4.3

Location (reference)	Case Definition	Denominator type	Specimen and diagnostic test	0–5 m	6–11 m	12–23 m	24–59 m	0–59 m
Beijing, China (2017–2018) (赵小娟 et al. 2018)	ARI–Fever	Census–derived estimate	TS; PCR	..	..	..	5.3	5.0
Oman (2012–2015) (Abdel-Hady et al. 2018)	ARI	Census–derived estimate	Respiratory specimen; PCR	..	..	..	..	0.8

Table A19–1f. IFV – Description of studies reporting hospitalisation rates of IFV–associated ALRI with hypoxaemia in children under five years (per 1,000 children per year) *†

Location (reference)	Case Definition	Denominator type	Specimen and diagnostic test	0–5 m	6–11 m	12–23 m	24–59 m	0–59 m
St. Elizabeth, Lwak, Asembo, Kenya; Rural (2010–2014) (Chaves and colleagues, unpublished)	sALRI	Census–derived estimate	NPS and OPS; PCR	0	7.8	2.4	0	1.3
Siaya County, Kenya; Rural (2010–2014) (Chaves and colleagues, unpublished)	sALRI	Census–derived estimate	NPS and OPS; PCR	1.2	1.5	1.4	0.6	0.9
Soweto, Gauteng, South Africa; urban (Mar 1998–Oct 2005) (Madhi and colleagues, unpublished)	sALRI	Defined population base	NPA; IFA	1.1	0.7	0.5	0.1	0.3
Amman, Jordan; urban (Mar 2010–Mar 2013) (Khuri–Bulos and colleagues, unpublished)	sALRI	Census–derived estimate	NS and TS; PCR	--	--	0	--	--
Manhiça, Mozambique; rural (Jan 2011–Jun 2014) (Bassat and colleagues, unpublished)	sALRI	Census–derived estimate	NPA; PCR	0	0.6	0.2	0	0.1
Kilifi, Kenya; rural and semi–urban (Jan 2007–Dec 2016) (Nokes and colleagues, unpublished)	sALRI	Census–derived estimate	NPS; PCR	0.4	0.3	0.2	0.1	0.1
Nha Trang city, Vietnam; urban and sub–urban (2008–2013) (Yoshida and colleagues, unpublished)	sALRI	Census–derived estimate	NP specimens; PCR	--	--	0.2	0.1	0.2
Pune district, India; rural (May 2009 – Apr 2013) (Hirve and colleagues, unpublished)	sALRI	Census–derived estimate	NPS; PCR	0	0	0.3	0	--
Ciudad de Buenos Aires, Argentina; urban (Jun 2008–Dec 2010) (Echavarria and colleagues, unpublished)	sALRI	Defined population base	NPA; IFA	--	--	1.1	0	0.3
Aurora, Colorado, United States; urban (Jan 2011–Oct 2015) (Simões and colleagues, unpublished)	sALRI	Census–derived estimate	--; --	--	--	0.3	0.1	0.2

* NPA: nasopharyngeal aspirate. NPS: nasopharyngeal swab. NPW: nasopharyngeal wash. OPS: oropharyngeal swab. PCR: polymerase chain reaction. IF: immunofluorescence. IFA: indirect immunofluorescence assay. DFA: direct fluorescent antibody. ELISA: enzyme-linked immunosorbent assay. HI: hemagglutination-inhibition assay. RIDT: rapid influenza diagnostic test. MN: micro-neutralization assay. TRFIA: time-resolved fluoroimmunoassay. sALRI: hospitalised ALRI with hypoxaemia, or ALRI in ICU or requiring MV. All: all diagnosis related to influenza (including influenza & pneumonia and other non-respiratory illnesses).

† Hospitalisation rates were adjusted for the proportion of testing in hospitalised ALRI patients where available.

Location (reference)	Case Definition	Denominator type	Specimen and diagnostic test	0–5 m	6–11 m	12–23 m	24–59 m	0–59 m
Region VI Buenos Aires Province, Argentina; urban /slums/semi–rural (2011–2013) (Polack and colleagues, unpublished)	sALRI AND SpO2 <93%	Census–derived estimate	NPA; PCR	0.7	1.3	0.6	--	--
Quetzaltnango, Guatemala (2010–2016) (McCracken and colleagues, unpublished)	sALRI	Census–derived estimate	NPS and OPS; PCR	1.5	0.8	0.6	0.1	0.4
Cuilapa, Santa Rosa, Guatemala (2010–2016) (McCracken and colleagues, unpublished)	sALRI	Census–derived estimate	NPS and OPS; PCR	1.8	0.6	0.8	0.1	0.5
Tagbilaran City, Bohol, Philipines; Dauis, Baclayon, Panglao, Cortes, Balilihan, Bohol, Philippines; mixed urban–rural (Jul 2000–Dec 2004) (Lucero and colleagues, unpublished)	sALRI	Defined population base	NPA; Viral culture	0.7	0	0.1	--	--
Valencia Region, Spain (2014–2017) (Mira Iglesias and colleagues, unpublished)	All	Census–derived estimate	NPS and NS; PCR	--	--	0	0	0.0
Buenos Aires, Argentina; urban (2009–2016) (Gentile and colleagues, unpublished)	sALRI	NA	NPA; PCR	--	--	3.2	1.1	2.5
Tone and Cinkasse districts, Togo; mixed urban–rural (Aug 2011–Oct 2013; Aug 2014–Jul 2015) (Moïsi and colleagues, unpublished)	sALRI	Census–derived estimate	NPA; PCR	--	--	--	--	0

Table A19–1g. IFV – Description of studies reporting hospitalisation rates of IFV–very severe ALRI in children under five years (per 1,000 children per year) *†

Location (reference)	Case Definition	Denominator type	Specimen and diagnostic test	0–5 m	6–11 m	12–23 m	24–59 m	0–59 m
France (2009–2013) (Bonmarin et al. 2015)	Flu AND ICU	Census–derived estimate	--	--	--	--	--	0
Australia (1997–2013) (Kaczmarek et al. 2016)	Flu AND ICU	Census–derived estimate	--	--	--	--	--	0
St. Elizabeth, Lwak, Asembo, Kenya; rural (2010–2014) (Chaves and colleagues, unpublished)	ALRI AND ICU; MV; danger signs	Census–derived estimate	NPS and OPS; PCR	0	5.2	2.4	0	1.0
Siaya County, Kenya; rural (2010–2014) (Chaves and colleagues, unpublished)	ALRI AND ICU; MV; danger signs	Census–derived estimate	NPS and OPS; PCR	1	1.3	1.4	0.5	0.8
Soweto, Gauteng, South Africa; urban (Mar 1998–Oct 2005) (Madhi and colleagues, unpublished)	ALRI AND ICU; MV; danger signs	Defined population base	NPA; IFA	0	0	0	0	0
Amman, Jordan; urban (Mar 2010–Mar 2013) (Khuri–Bulos and colleagues, unpublished)	ALRI AND ICU; MV; danger signs	Defined population base	NS and TS; PCR	--	--	0	--	--
Manhiça, Mozambique; rural (Jan 2011–Jun 2014) (Bassat and colleagues, unpublished)	ALRI AND ICU; MV; danger signs	Census–derived estimate	NPA; PCR	0	0.6	0.2	0	0.1
Kilifi, Kenya; rural and semi–urban (Jan 2007– Dec 2016) (Nokes and colleagues, unpublished)	ALRI AND ICU; MV; danger signs	Census–derived estimate	NPS; PCR	0.8	0.4	0.3	0.1	0.3

* NPA: nasopharyngeal aspirate. NPS: nasopharyngeal swab. NPW: nasopharyngeal wash. OPS: oropharyngeal swab. NS: nasal swab. TS: throat swab. PCR: polymerase chain reaction. RT-PCR: reverse transcriptase polymerase chain reaction. IFA: indirect immunofluorescence assay. DFA: direct fluorescent antibody. ELISA: enzyme-linked immunosorbent assay. IF: immunofluorescence. HI: hemagglutination-inhibition assay. RIDT: rapid influenza diagnostic test. SPIA: Solid-phase immunoassay. EIA: enzyme immunoassay. MN: micro-neutralization assay. TRFIA: time-resolved fluoroimmunoassay. ICU: intensive care unit. MV: mechanical ventilation. All: all diagnosis related to influenza (including influenza & pneumonia and other non-respiratory illnesses). Flu: laboratory-confirmed influenza.

† Hospitalisation rates were adjusted for the proportion of testing in hospitalised ALRI patients.

Location (reference)	Case Definition	Denominator type	Specimen and diagnostic test	0–5 m	6–11 m	12–23 m	24–59 m	0–59 m
Muang District, Nakhon Phanom Province, Thailand (PERCH); rural (2012–2013) (O'Brien and colleagues, unpublished)	ALRI AND chest wall indrawing AND danger signs	Census–derived estimate	NP/OP and induced sputum; PCR	..	..	0	0.1	0.1
Muang District, Sa Kaeo Province, Thailand; rural (2012–2013) (O'Brien and colleagues, unpublished)	ALRI AND chest wall indrawing AND danger signs	Census–derived estimate	NP/OP and induced sputum; PCR	..	..	0.4	0.1	0.1
Nha Trang city, Vietnam; urban and sub–urban (2008–2013) (Yoshida and colleagues, unpublished)	ALRI AND ICU; MV; danger signs	Census–derived estimate	NP specimens; PCR	..	..	0	0	0
Basse, Upper River Region, The Gambia (PERCH); rural (Nov 2011–Nov 2013) (O'Brien and colleagues, unpublished)	ALRI AND chest wall indrawing AND danger signs	Census–derived estimate	NPS/OPS, induced sputum; PCR	0	0.1	0	0.1	0
Bersheba, Israel (Sep–Mar 2011–2016) (Katz and colleagues, unpublished)	ARI; Fever AND ICU	Clalit Health Services Electronic Medical Records	OPS and NS; PCR	0.3	0.1	0	0	0.1
Nakhon Phanom and Sa Kaeo Provinces, Thailand; rural (Jan 2005–Dec 2011) (Thamtithiwat and colleagues, unpublished)	Intubation or SpO2 <80 mmHg	Census–derived estimate	NPS; PCR	0.2	0.7	0.5	0.1	0.3
David City, Panama (2014–2016) (Jara and colleagues, unpublished)	ALRI; ICU/MV/with danger signs	Census–derived estimate	NPS or OPS; PCR	..	..	0.4	0	0.6
Ciudad de Buenos Aires, Argentina; urban (Jun 2008–Dec 2010) (Echavarria and colleagues, unpublished)	ALRI AND ICU; MV; danger signs	Defined population base	NPA; IFA	..	..	0	0	0
Turku, Finland; urban (Jan 2010–Jun 2012) (Heikkinen and colleagues, unpublished)	ALRI AND ICU; MV; danger signs	Census–derived estimate	NS; TRFIA	0.3	0	0.2	0	0.1
Aurora, Colorado, USA; urban (Jan 2011–Oct 2015) (Simões and colleagues, unpublished)	ALRI AND ICU; MV; danger signs	Census–derived estimate	..	..	..	0	0	0
Region VI Buenos Aires Province, Argentina; urban /slums/semi–rural (2011–2013)	ALRI AND ICU; MV; danger signs	Census–derived estimate	NPA; PCR	0.3	0.4	0	..	..

Location (reference)	Case Definition	Denominator type	Specimen and diagnostic test	0–5 m	6–11 m	12–23 m	24–59 m	0–59 m
(Polack and colleagues, unpublished)								
Quetzaltnango, Guatemala (2010–2016) (McCracken and colleagues, unpublished)	ALRI; ICU/MV/with danger signs	Census–derived estimate	NPS and OPS; PCR	1.5	0.8	0.5	0.1	0.4
Cuilapa, Santa Rosa, Guatemala (2010–2016) (McCracken and colleagues, unpublished)	ALRI; ICU/MV/with danger signs	Census–derived estimate	NPS and OPS; PCR	1.8	0.6	0.8	0.1	0.5
Tagbilaran City, Bohol, Philipines; Dauis, Baclayon, Panglao, Cortes, Balilihan, Bohol, Philippines; mixed urban–rural (Jul 2000–Dec 2004) (Lucero and colleagues, unpublished)	ALRI; ICU/MV/with danger signs	Defined population base	NPA; Viral culture	0.7	0	0	..	..
Valencia Region, Spain (2014–2017) (Mira Iglesias and colleagues, unpublished)	All AND ICU; MV; danger signs	Census–derived estimate	NPS and NS; PCR	..	..	0	0	0
Buenos Aires, Argentina; urban (2009–2016) (Gentile and colleagues, unpublished)	ALRI AND ICU; MV; danger signs	Census–derived estimate	NPA; PCR	..	..	0.6	0.2	0.4
Concepcion, Chile; mixed urban/rural (2012–2013) (Fasce and colleagues, unpublished)	ALRI AND ICU; MV; danger signs	Census–derived estimate	NPA, NPS; PCR	..	..	0.1	0	0.1
Iquique, Chile; mixed urban–rural (2012–2013) (Fasce and colleagues, unpublished)	ALRI AND ICU; MV; danger signs	Census–derived estimate	NPA; PCR	..	..	0	0.1	0.1
Denmark (2009–10; 2010–11) (Gubbels et al. 2013)	Flu AND ICU	Sentinel surveillance	..; PCR	..	..	..	..	0
Taiwan (June 2009–March 2011) (Chuang et al. 2012)	Flu AND ICU	Census–derived estimate	NS and TS; PCR, viral culture, and HI	..	..	..	..	0.1
Germany (Jan 2005–Dec 2012) (Von Der Beck et al. 2017)	ARI AND MV	Census derived estimate	..	..	..	..	..	0
Tone and Cinkasse districts, Togo; mixed urban–rural (Aug 2011–Oct 2013; May 2014–Jul 2015) (Moïsi and colleagues, unpublished)	ALRI AND ICU; MV; danger signs	Census–derived estimate	NPA; PCR	..	..	..	..	0

Location (reference)	Case Definition	Denominator type	Specimen and diagnostic test	0–5 m	6–11 m	12–23 m	24–59 m	0–59 m
Spain (2010–2016) (Oliva et al. 2018)	ALRI AND ICU	Census–derived estimate	Respiratory swab; --	--	--	--	--	0

Table A19–1h. IFV – Description of studies reporting IFV–ALRI in–hospital case fatality ratios (hCFRs) in children under five years*

Location (reference)	Case definition	Specimen and diagnostic test	0–5 m		6–11 m		12–59 m		0–59 m	
			Cases	hCFR (%)	Cases	hCFR (%)	Cases	hCFR (%)	Cases	hCFR (%)
Bondo district, Kenya (Jun 2007–May 2009) (Nair et al. 2011)	ALRI	NPS or OPS; PCR	--	--	--	--	--	--	67	4.5
Multistate, USA (Oct–Apr 2003–2008) (Dawood et al. 2010)	ALRI	NPS or OPS; Viral culture, DFA, IFA, RIDT, PCR	1121	0.3	--	--	--	--	3023	0.2
Gipuzoka, Spain (Jul 2001–Jun 2004) (Montes et al. 2005)	ARI	NPA; Viral culture and PCR	--	--	--	--	--	--	70	0
Leicester, United Kingdom (Oct 2001–Jun 2002) (Nicholson et al. 2006)	ARI	Nasal and throat swabs; PCR	--	--	--	--	--	--	33	0
Hong Kong (July 1997– June 1999) (Nelson et al. 2007)	ARI	NPA; Viral culture and serology	--	--	--	--	--	--	5471	0.1
South Australia, Australia (1996–2006) (D'Onise and Raupach 2008)	ARI	--; Viral Culture, and PCR	--	--	--	--	--	--	626	0.6
Salt Lake County, Utah, USA (Jul 2001–Jun 2004) (Ampofo et al. 2006)	ALRI	NPA; DFA	92	0	--	--	--	--	325	0.3
Philadelphia, USA (Jul 2000– Jun 2004)(Coffin et al. 2007)	All	Nasal aspirates; SPIA, DFA and viral culture	--	--	--	--	--	--	573	0.9
Jordan, Oman, and Egypt (Oct 2007–Nov 2009) (Nair et al. 2011)	ALRI; Chest wall indrawing	--; PCR	--	--	--	--	--	--	77	1.3
Hong Kong (Jan–Jun 2005) (Kwong et al. 2009)	ARI; Fever	--; RIDT	--	--	--	--	--	--	86	1.2
Canada (2003–2004) (Moore et al. 2006)	ARI; Fever	--; Culture or DFA	116	0	--	--	--	--	423	0.2
Parana State, Brazil (Jan 1996–Dec 2001) (Coelho et al. 2007)	ARI	NPA or BAL; IFA and culture	--	--	--	--	--	--	45	6.7

* NPA: nasopharyngeal aspirate. NPS: nasopharyngeal swab. NPW: nasopharyngeal wash. OPS: oropharyngeal swab. BAL: bronchoalveolar lavage. PCR: polymerase chain reaction. IFA: indirect immunofluorescence assay. DFA: direct fluorescent antibody. ELISA: enzyme-linked immunosorbent assay. IF: immunofluorescence. HI: hemagglutination-inhibition assay. RIDT: rapid influenza diagnostic test. SPIA: Solid-phase immunoassay. EIA: enzyme immunoassay. MN: micro-neutralization assay. TRFIA: time-resolved fluoroimmunoassay. ARI: any respiratory infections/symptoms (acute one of cough, sore throat, shortness of breath, coryza); ICD-codes for influenza & pneumonia (excluding non-respiratory manifestations); or acute infections (fever or <35 degree C) with any respiratory signs. ALRI: physician-diagnosed pneumonia and/or bronchiolitis, or WHO definition for ALRI applied by a health worker requiring hospitalisation. All: all diagnosis related to influenza (including influenza & pneumonia and other non-respiratory illnesses).

Location (reference)	Case definition	Specimen and diagnostic test	0–5 m		6–11 m		12–59 m		0–59 m	
			Cases	hCFR (%)	Cases	hCFR (%)	Cases	hCFR (%)	Cases	hCFR (%)
Kuala Lumpur, Malaysia (2002–2007) (Sam et al. 2010)	ARI	··; DFA and culture	··	··	··	··	73	2.7	116	2.6
Santa Rosa, Guatemala (Jan 2008–Apr 2009) (Nair et al. 2011)	ARI	NPS or OPS; PCR	··	··	··	··	··	··	8	25
Islamabad Pakistan (Mar 2011–Apr 2012) (Bashir et al. 2017)	ALRI	NPS or OPS; PCR	··	··	··	··	··	··	··	··
Izmir, Turkey (Oct 2014–May 2015) (Kanik et al. 2016)	ALRI	NPS; PCR	··	··	··	··	··	··	··	··
Australia (Jan 2011–Dec 2013) (J. Li-Kim-Moy et al. 2017)	ARI	··; PCR	99	0	80	0	297	0	476	0
Germany (Jan 2005–Dec 2012) (Von Der Beck et al. 2017)	ARI	··	··	··	··	··	··	··	6328	0.4
Turkey (Dec 2012–March 2016) (Acar et al. 2017)	ARI; Fever	NPS; PCR	8	0	··	··	··	··	61	3.3
Egypt, Jordan, Oman, Qatar and Yemen (2007–2014) (Horton et al. 2017a)	ARI	NPS and OPS; PCR	··	··	··	··	··	··	762	2.5
Multi–country (2010–2014) (Dananche et al. 2018)	ALRI	Nasal swab and nasal aspirate; PCR	··	··	··	··	··	··	86	3.5
Bucharest, Romania (2016–2017) (Draganescu et al. 2018)	ARI	NPS or nasal swab; PCR	··	··	··	··	··	··	58	1.7
Multi–counrty (2013) (El Omeiri et al. 2018)	ALRI–Fever	Combined nasal and OP swab or pharyngeal wash; PCR	··	··	··	··	··	··	··	··
Kutaisi, Georgia (2014–2017) (Machablishvili et al. 2018)	ARI–Fever	Oral and nasal swab; PCR	··	··	··	··	165	1.2	242	0.8
Maputo, Mozambique (2014–2016) (Nguenha et al. 2018)	ARI–Fever	NPS or OPS; PCR	9	11.1	14	0	40	0	63	1.6
Spain (2010–2016) (Oliva et al. 2018)	ALRI	Respiratory swab; PCR	··	··	··	··	··	··	426	0.9
Deli Serdang,Balikpapan, Gunung Kidul, Indonesia (2013–2016) (Susilarini et al. 2018)	ARI–Fever	Respiratory specimen; PCR	··	··	··	··	··	··	114	0
Catalonia, Spain (2014–2016) (Torner et al. 2018)	ALRI	NPS; PCR and culture	··	··	··	··	··	··	167	1.2
Shenzhen, China (2014–2015) (张锐沐 2016)	ALRI	NPS; DFA	··	··	··	··	··	··	127	0.8

Location (reference)	Case definition	Specimen and diagnostic test	0–5 m		6–11 m		12–59 m		0–59 m	
			Cases	hCFR (%)	Cases	hCFR (%)	Cases	hCFR (%)	Cases	hCFR (%)
Wuhan, China (2016–2017) (朱芮 et al. 2018)	ARI	pharyngeal specimen; PCR	..	..	..	..	..	..	..	..
Siaya County, Kenya; rural (2010–2014) (Chaves and colleagues, unpublished)	ALRI	NPS or OPS; PCR	9	0	10	0	38	2.6	57	1.8
Tone and Cinkasse districts, Togo; mixed urban–rural (Aug 2011–Oct 2013; Aug 2014–July 2015) (Moïsi and colleagues, unpublished)	ALRI	NPA; PCR	1	0	5	0	14	0	20	0
Soweto, Gauteng, South Africa; urban (Mar 1998–Oct 2005) (Madhi and colleagues, unpublished)	ALRI	NPA; IFA	28	3.6	20	10	50	2	98	4.1
Amman, Jordan; urban (Mar 2010–Mar 2013) (Khuri–Bulos and colleagues, unpublished)	ALRI	Nasal/throat swabs; PCR	35	5.7	22	0	..	..	..	..
Manhiça, Mozambique; rural (Jan 2011–Jun 2014) (Bassat and colleagues, unpublished)	ALRI	NPA; PCR	5	0	7	14.3	11	0	23	4.3
Kilifi, Kenya; rural and semi–urban (Jan 2007– Dec 2016) (Nokes and colleagues, unpublished)	ALRI	NPS; PCR	33	6.1	26	11.5	59	3.4	118	5.9
Muang District, Nakhon Phanom Province, Thailand (PERCH); rural (2012–2013) (O'Brien and colleagues, unpublished)	ALRI	NP/OP and induced sputum; PCR	..	..	1	0	1	0	2	0
Muang District, Sa Kaeo Province, Thailand; rural (2012–2013) (O'Brien and colleagues, unpublished)	ALRI	NP/OP and induced sputum; PCR	..	..	..	..	3	33.3	3	33.3
Nha Trang city, Vietnam; urban and sub–urban (2008–2013) (Yoshida and colleagues, unpublished)	ALRI	NP specimens; PCR	4	0	6	0	35	0	45	0
Berlin, Germany; urban (2010–2014) (Rath and colleagues, unpublished)	ALRI	NPS; PCR	31	0	22	0	98	0	151	0
Basse, Upper River Region, Gambia (PERCH); rural (Nov 2011–Nov 2013) (O'Brien and colleagues, unpublished)	ALRI	NPS, OPS, induced sputum; PCR	17	0	4	0	12	0	33	0

Location (reference)	Case definition	Specimen and diagnostic test	0–5 m		6–11 m		12–59 m		0–59 m	
			Cases	hCFR (%)	Cases	hCFR (%)	Cases	hCFR (%)	Cases	hCFR (%)
Nakhon Phanom and Sa Kaeo Province, Thailand; rural (Jan 2005–Dec 2011) (Thamtithiwat and colleagues, unpublished)	ALRI	NPS; PCR	34	0	110	0	559	0.2	703	0.1
Pune district, India; rural (May 2009–Apr 2013) (Hirve and colleagues, unpublished)	ALRI	NPS; PCR	..	..	2	0	2	0	4	0
David City, Panama (2014–2016) (Jara and colleagues, unpublished)	ALRI	NPS or OPS; PCR	14	21.4	15	13.3	30	0	59	8.5
Ciudad de Buenos Aires, Argentina; urban (Jun 2008–Dec 2010) (Echavarria and colleagues, unpublished)	ALRI	NPA; IFA	5	0	2	0	5	0	12	0
Turku, Finland; urban (Jan 2010–Jun 2012) (Heikkinen and colleagues, unpublished)	ALRI	Nasal swabs; TRFIA	12	0	4	0	12	8.3	28	3.6
Aurora, Colorado, United States; urban (Jan 2011–Oct 2015) (Simões and colleagues, unpublished)	ALRI	..	134	0	106	1.9	390	0.8	630	0.8
Paarl, Western Province, South Africa (June 2012–Dec 2016) (Zar and colleagues, unpublished)	ALRI	NPS; PCR	10	10	4	0	4	0	18	5.6
Region VI Buenos Aires Province, Argentina; urban /slums/semi–rural (2011–2013) (Polack and colleagues, unpublished)	ALRI; Wheezing; SpO2 <93%	NPA; PCR	26	3.8	20	0	..	..	..	..
Quetzaltnango, Guatemala (2010–2016) (McCracken and colleagues, unpublished)	ALRI	NPS and OPS; PCR	36	0	19	5.3	46	2.2	101	2.0
Cuilapa, Santa Rosa, Guatemala (2010–2016) (McCracken and colleagues, unpublished)	ALRI	NPS and OPS; PCR	17	11.8	6	33.3	27	7.4	50	12.0
Tagbilaran City, Bohol, Philipines; Dauis, Baclayon, Panglao, Cortes, Balilihan, Bohol, Philippines; mixed urban–rural (Jul 2000–Dec 2004) (Lucero and colleagues, unpublished)	ALRI	NPA; Viral culture	11	9.1	19	0	..	..	..	..

Location (reference)	Case definition	Specimen and diagnostic test	0–5 m		6–11 m		12–59 m		0–59 m	
			Cases	hCFR (%)	Cases	hCFR (%)	Cases	hCFR (%)	Cases	hCFR (%)
Valencia Region, Spain (2014–2017) (Mira Iglesias and colleagues, unpublished)	All	NPS and nasal swabs; RT–PCR	39	2.6	16	0	71	0	126	0.8
Buenos Aires, Argentina; urban (2009–2016) (Gentile and colleagues, unpublished)	ALRI	NPA; PCR	21	4.8	29	0	49	4.1	99	3.0
Karachi, Sind, Pakistan (Jan 2009–Feb 2018) (Abbas and colleagues, unpublished)	ALRI	NP secretions; PCR	--	--	--	--	13	38.5	22	31.8
Soweto, Gauteng, South Africa (2015–2017) (Madhi and colleagues, unpublished)	ALRI; Sepsis	NPS; PCR	45	0	61	0	47	0	153	0
Rabat, Morocco (Nov 2010–Dec 2011) (Bassat and colleagues, unpublished)	ALRI	NPA; PCR	3	0	9	0	16	6.2	28	3.6
Lusaka, Zambia (2011–2013) (O'Brien and colleagues, unpublished)	ALRI	NPS, OPS, Induced sputum; --	11	27.3	7	14.3	13	15.4	31	19.4
Soweto, South Africa (2011–2013) (O'Brien and colleagues, unpublished)	ALRI	NPS, OPS, Induced sputum; --	18	0	15	6.7	21	4.8	53	3.8
Matlab, Bangladesh (2012–2013) (O'Brien and colleagues, unpublished)	ALRI	NPS, OPS, Induced sputum; --	3	0	4	0	0	--	7	0
Dhaka, Bangladesh (2012–2013) (O'Brien and colleagues, unpublished)	ALRI	NPS, OPS, Induced sputum; --	1	0	0	--	2	0	3	0
Klerksdorp, North West Province, South Africa; peri–urban (2013–2015) (Cohen and colleagues, unpublished)	ALRI; Sepsis	NPA; PCR	5	0	7	0	18	0	30	0
Pietermaritzburg, Kwa–Zulu Natal Province, South Africa; peri–urban (2013–2015) (Cohen and colleagues, unpublished)	ALRI; Sepsis	NPA; PCR	9	11.1	14	0	15	0	38	2.6
Soweto, Gauteng, South Africa; urban (2009–2012) (Cohen and colleagues, unpublished)	ALRI; Sepsis	NPA; PCR	70	1.4	61	0	104	1	235	0.9
Concepcion, Chile; mixed urban/rural (2012–2013) (Fasce and colleagues, unpublished)	ALRI	NPA and NPS; PCR	12	8.3	6	0	18	0	36	2.8

Location (reference)	Case definition	Specimen and diagnostic test	0–5 m		6–11 m		12–59 m		0–59 m	
			Cases	hCFR (%)	Cases	hCFR (%)	Cases	hCFR (%)	Cases	hCFR (%)
Iquique, Chile; mixed urban–rural (2012–2013) (Fasce and colleagues, unpublished)	ALRI	NPA; PCR	5	0	9	0	17	0	31	0

Table A19–2a. hMPV– Description of included studies reporting incidence rates of hMPV–ALRI cases (per 1,000 children per year) in children under five years. *

Location (reference)	Case Definition	Denominator type	Specimen and diagnostic test	0–5 m	6–11 m	12-23 m	24-59 m	0–59 m
Paarl, South Africa (Jun 2012–Dec 2017) (Zar and colleagues, unpublished)	ALRI	Defined population estimates	NPS; PCR	60.4	37.3	23	12	24.5
Oshikhandass, Pakistan (Dec 2012–Nov 2013) (Rasmussen and colleagues, unpublished)	ALRI	Defined population estimates	NPS; PCR	0	0	20.5	13.6	12.3
Kamalapur, Bangladesh (2013–2014) (Brooks and colleagues, unpublished)	ALRI	Defined population estimates	NPW; PCR	6.9	12.9	37.5	38.2	20.7
Bhaktapur, Nepal (2004–2007) (Strand and colleagues, unpublished)	ALRI	Defined population estimates	NPA; PCR	28.8	27.5	23.2	--	--
Faridabad, India (Aug 2012–Aug 2014) (Krishanan and colleagues, unpublished)	ALRI	Census derived population	OP and nasal specimens; PCR	96	55.4	41.3	10.8	27.7
San Marcos, Cajamarca, Peru; rural (Mar 2009 – Sep 2011) (Wu et al. 2015)	ALRI–Fever/ALRI	Defined population estimates	NS; PCR	--	--	--	--	--
Nashville, USA (1976–2001) (Williams et al. 2004)	ALRI	Defined population estimates	NW; PCR and culture	--	--	--	--	17.5
Brisbane, Australia (Sep 2010–Oct 2014) (Sarna et al. 2018)	ALRI	Defined population base	NS; PCR	--	--	--	--	--
Perth, Australia (Jul 1996–Jul 1999) (Kusel et al. 2006)	ALRI	Defined population base	NPA; PCR	--	--	--	--	--

* ALRI: acute lower respiratory infections according to WHO IMCI definition. ALRI–fever: ALRI with fever. NPS: nasopharyngeal swab. PCR: polymerase chain reaction. NPW: nasopharyngeal wash. NPA: nasopharyngeal aspirate. OP specimens: oropharyngeal specimens. NS: nasal swab. NW: nasal wash.

Table A19–2b. hMPV– Description of included studies reporting incidence rates of hMPV–severe ALRI cases (per 1,000 children per year) in children under five years*

Location (reference)	Case Definition	Denominator type	Specimen and diagnostic test	0–5 m	6–11 m	12-23 m	24-59 m	0–59 m
Karachi, Pakistan (Oct 2011–July 2014) (Ali et al. 2016)	sALRI	Defined population estimates	NPS; PCR	2.5	--	--	--	--
Paarl, South Africa (Jun 2012–Dec 2017) (Zar and colleagues, unpublished)	sALRI	Defined population estimates	NPS; PCR	49.5	29	12.6	9.0	18.0
Kamalapur, Bangladesh (2014) (Brooks and colleagues, unpublished)	sALRI	Defined population estimates	NPW; PCR	1.2	1.8	0	2.2	1.3
Faridabad, India (Aug 2012–Aug 2014) (Krishanan and colleagues, unpublished)	sALRI	Census derived population	OP and nasal specimens; PCR	55.6	31.1	26.4	5.7	16.8

* sALRI: severe acute lower respiratory infections according to 2005 WHO IMCI. NPS: nasopharyngeal swab. PCR: polymerase chain reaction. NPW: nasopharyngeal wash. OP specimens: oropharyngeal specimens.

Table A19–2c. hMPV – Description of included studies reporting hospitalisation rates of hMPV–associated ALRI cases in children younger than five years*†

Location (reference)	Case Definition	Denominator type	Specimen and test	0–5 m	6–11 m	12-23 m	24-59 m	0–59 m
NVSN sites, USA (Nov–May, 2003–2009) (Edwards et al. 2013)	Fever; ARI	Census derived population	NS and TS; PCR	3	2	1.2	0.5	1
Soweto, South Africa (Feb 2009–Dec 2012) (Groome et al. 2015)	ALRI	Census derived estimate	NPA; PCR	..	..	1.7	0.3	1.8
Sa Kaeo and Nakhon Phanom, Thailand (2005–2010) (Hasan et al. 2014)	ARI	Census derived population	NPS and serum specimens; PCR, serologic test and culture	1.8	..	..	1.3	2
Memphis, Nashville, and Salt Lake City (EPIC), USA (Jan 2010–June 2012) (Jain et al. 2015)	ALRI	Census derived population	NPS and OPS; PCR and serologic testing	..	..	..	0.4	0.6
Rochester, New York; Nashville, Tennessee (NVSN), USA (Aug 2000–Sep 2001) (Mullins et al. 2004)	Fever; ARI	Census derived population	NS and TS; PCR	..	..	1.3	0.1	0.6
Leicester, UK (Oct 2001–June 2002) (Nicholson et al. 2006)	All	Census derived population	Combined NTS; PCR	..	..	2.4	..	..
Salt Lake County, Utah, USA (July 2007–June 2013) (Davis et al. 2016b)	ALRI	Census derived population	NA; DFA and PCR	2	2.5	1.8	0.5	1.1
Haryana, India (Aug 2009–July 2011) (Broor et al. 2014b)	All	Census derived population	NS and TS; PCR	..	..	..	..	0.2
Santa Rosa, Quetzaltenango, Guatemala (Nov 2007–Dec 2012) (McCracken et al. 2014)	ALRI	Census derived population	NPS and OPS; PCR	2.1	..	..	0.3	1
Gipuzkoa, Spain; (July 2004–June 2007) (Cilla et al. 2009)	ARI; ARI–Fever	Census derived population	NPA; PCR and culture	6.8	3.5	1.8	..	..

* ARI: acute respiratory infections requiring hospital admission. ALRI: physician diagnosed acute lower respiratory infections requiring hospital admission. ARI–Fever: hospitalised acute respiratory infections with fever. ALRI–Fever: hospitalised acute lower respiratory infections with fever. All: all diagnosis related to influenza (including influenza & pneumonia and other non-respiratory illnesses). NS: nasal swab. TS: throat swab. PCR: polymerase chain reaction. NPA: nasopharyngeal aspirate. NPS: nasopharyngeal swab. OPS: oropharyngeal swab. NPW: nasopharyngeal wash. IFA: indirect immunofluorescence assay. DFA: direct immunofluorescence assay.
† ..: not available. some included did not provide data for any of these listed age groups but provided data for other age groups.

Location (reference)	Case Definition	Denominator type	Specimen and test	0–5 m	6–11 m	12-23 m	24-59 m	0–59 m
Nakhon Phanom, Thailand (Jan 2012–Dec 2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	Census derived population	NP/OP and induced sputum; PCR	..	..	0.6	0	0.1
Sa Kaeo, Thailand (Jan 2012–Dec 2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	Census derived population	NP/OP and induced sputum; PCR	..	..	0	0.1	0.1
Kawayan and Caibiran, Philippines (Feb 2014–Jun 2016) (Oshitani and colleagues, unpublished)	ALRI	Defined population estimates	NPS; PCR	12.1	2.2	2.0	1.2	2.2
Nha Trang city, Viet Nam (Jan 2007–Dec 2014) (Yoshida and colleagues, unpublished)	ALRI	Census derived population	NPS; PCR	..	..	0.8	0.2	0.6
Paarl, South Africa (Jun 2012–Dec 2017) (Zar and colleagues, unpublished)	ALRI	Defined population estimates	NPS; PCR	18	10.9	3.1	1.3	5.5
Manhiça, Mozambique (Jan–Dec 2011) (Bassat and colleagues, unpublished)	ALRI	Census derived population	NPA; PCR	1.1	2.1	0.4	0.3	0.6
Concepcion, Chile (2012–2013) (Fasce and colleagues, unpublished)	ALRI	Census derived population	NPA; IFA	..	..	0.3	0.1	0.3
Kamalapur, Bangladesh (2013–2014) (Brooks and colleagues, unpublished)	ALRI	Defined population estimates	NPW; PCR	1.5	1.9	1.6	2.8	1.8
Ciudad de Buenos Aires, Argentina (Jun 2008–Dec 2010) (Echavarria and colleagues, unpublished)	ARI	Defined population estimates	NPA; DFA	0	..	..	0.5	0.6
Multiple sites, Philippines (Jul 2000–Dec 2004) (Lucero and colleagues, unpublished)	ALRI	Defined population estimates	NPA and NPS; Viral culture	4.4	6.4	2.6	..	..
Soweto, Gauteng, South Africa (2015–2017) (Nunes and colleagues, unpublished)	ALRI	Census derived population	NPS; PCR	..	..	1	0.4	0.9
Soweto, Gauteng, South Africa (Jan 2000–Dec 2002) (Madhi and colleagues, unpublished)	ALRI	Defined population estimates	NPA; PCR	9.6	7.4	2.6	1.1	2.6
Pune, India (May 2009–Apr 2013) (Hirve and colleagues, unpublished)	ALRI	Census derived population	NPS; PCR	1.1	0.9	1	0.3	0.5
Amman, Jordan (Mar 2010–Mar 2013) (Khuri-Bulos and colleagues, unpublished)	ALRI	Census derived population	NS and TS; PCR	1.5	1	0.4	..	..
Kilifi, Kenya (Jan 2007– Dec 2017) (Nokes and colleagues, unpublished)	ALRI	Census derived population	NPS; PCR	3.3	3.4	0.9	0.3	1.1

Location (reference)	Case Definition	Denominator type	Specimen and test	0–5 m	6–11 m	12-23 m	24-59 m	0–59 m
Valencia Region, Spain (2014–2017) (Mira Iglesias and colleagues, unpublished)	All	Census derived population	NPS and NS; PCR	..	..	0.3	0.1	0.4
Buenos Aires, Argentina (May 2011–Aug 2013) (Polack and colleagues, unpublished)	ALRI	Census derived population	NPA; PCR	3.8	3.5	0.7	..	..
Klerksdorp, South Africa (2010–2015) (Cohen and colleagues, unpublished)	ALRI	Census derived population	NPA; PCR	1.8	1	0.6	0.1	0.5
Pietermaritzburg, Kwa–Zulu Natal Province, South Africa (2010–2015) (Cohen and colleagues, unpublished)	ALRI	Census derived population	NPA; PCR	2.2	1.6	0.5	0.2	0.6
NVSN sites, USA (Oct 2001– Sep 2003) (Williams et al. 2004)	ARI–Fever; Fever	Census derived population	NS and TS; PCR and culture	..	..	..	..	1.2
San Marcos, Cajamarca, Peru; rural (Mar 2009 –Sep 2011) (Wu et al. 2015)	ALRI–Fever/ALRI	Defined population estimates	NS; PCR	..	..	..	..	..
Sør–Trøndelag County, Norway (Nov 2006–July 2015) (Moe et al. 2017b)	ALRI	Census derived estimates	NPA; PCR	..	..	..	..	1.8
Manhica, Mozambique (Sep 2006–Sep 2007) (O'Callaghan-Gordo et al. 2011)	ALRI	Census derived estimate	NPA; PCR	..	..	..	..	1.8
Asembo, Kenya (Mar 2007–Feb 2008) (Feikin et al. 2013)	ALRI	Census derived estimate	NPS or OPS; PCR	..	..	..	..	14.6
Bangladesh (2010–2014) (Homaira and colleagues, unpublished)	ARI–Fever; ALRI	Census derived population	NS and TS; PCR	..	..	..	..	1.1

Table A19–2d. Description of included studies reporting hCFRs (%) of hMPV–ALRI cases in children under five years*

Location (reference)	Case definition	Specimen and test	0–5 m		6–11 m		12–59 m		0–59 m	
			Cases (No.)	hCFR (%)	Cases (No.)	hCFR (%)	Cases (No.)	hCFR (%)	Cases (No.)	hCFR (%)
Seoul, Korea (Dec 2003–Feb 2005) (Chung et al. 2006)	ARI	--; PCR	3	0	7	0	18	5.6	25	4.0
Gipuzkoa, Spain; (July 2004–June 2007) (Cilla et al. 2009)	ARI; ARI–Fever	NPA; PCR and culture	--	--	--	--	--	--	--	--
Trondheim, Norway (Nov 2002–April 2003) (Dollner et al. 2004)	ARI	NPA; PCR	--	--	--	--	--	--	--	--
Madrid, Spain (Oct 2000–June 2003) (García-García et al. 2006)	ARI	NPA; PCR	--	--	--	--	--	--	--	--
Iowa, USA (Oct 2001–May 2004) (Gray et al. 2006)	ARI	mainly NW; PCR	2	0	3	0	14	7.1	15	6.7
Columbus, Ohio, USA (June 2007–June 2010) (Hahn et al. 2013)	ALRI	--; DFA	--	--	--	--	--	--	--	--
Yukon Kuskokwim Delta, USA (Oct 2005–Sep 2007) (Singleton et al. 2010)	ALRI	NP specimens; PCR	--	--	--	--	--	--	--	--
NVSN sites, USA (Oct 2001– Sep 2003)(Williams et al. 2010)	ARI–Fever; Fever	NS and TS; PCR and culture	--	--	--	--	--	--	42	0
Salt Lake County, Utah, USA (July 2007–June 2013) (Davis et al. 2016a)	ALRI	--; DFA and PCR	129	0.8	--	--	--	--	725	0.3
Hiroshima, Japan (37712) (Takao et al. 2003)	ALRI	NPA; PCR	--	--	--	--	--	--	7	0
Sør–Trøndelag County, Norway (Nov 2006–July 2015) (Moe et al. 2017a)	ALRI	NPA; PCR	29	0	34	0	97	1	160	0.6
Valencia Region, Spain (2014–2017) (Mira Iglesias and colleagues, unpublished)	All	NPS and NS; PCR	29	0	10	0	17	0	56	0
Berlin, Germany (Jan 2010–Dec 2014) (Rath and colleagues, unpublished)	ALRI	NPS; PCR	27	3.7	27	0	78	0	132	0.8

* ARI: acute respiratory infections requiring hospital admission. ALRI: physician diagnosed acute lower respiratory infections requiring hospital admission. ARI–Fever: hospitalised acute respiratory infections with fever. ALRI–Fever: hospitalised acute lower respiratory infections with fever. All: all diagnosis related to influenza (including influenza & pneumonia and other non-respiratory illnesses). NS: nasal swab. TS: throat swab. PCR: polymerase chain reaction. NPA: nasopharyngeal aspirate. NPS: nasopharyngeal swab. NW: nasopharyngeal wash. OPS: oropharyngeal swab. NPW: nasopharyngeal wash. BAL: bronchoalveolar lavage. IFA: indirect immunofluorescence assay. DFA: direct immunofluorescence assay.

Location (reference)	Case definition	Specimen and test	0–5 m		6–11 m		12–59 m		0–59 m	
			Cases (No.)	hCFR (%)	Cases (No.)	hCFR (%)	Cases (No.)	hCFR (%)	Cases (No.)	hCFR (%)
Aurora, Colorado, United States of America (2010–2016) (Simões and colleagues, unpublished)	ALRI	NW; PCR (and DFA)	106	0	93	1.1	432	0	631	0.2
Islamabad, Pakistan (March 2011–April 2012) (Bashir et al. 2017)	ALRI	NPS or OPS; PCR	..	..	..	..	..	..	..	..
Haryana, India (Aug 2009–July 2011) (Broor et al. 2014a)	All	NS and TS; PCR	..	..	..	..	..	..	3	0
São Paulo city, Brazil (March 2008–Feb 2010) (Durigon et al. 2015)	ARI	NPA; PCR	..	..	..	..	..	..	..	..
Takeo Province and Kampong Cham Province, Cambodia (April 2007–Feb 2010) (Guerrier et al. 2013)	ALRI	NPA; PCR	..	..	..	..	..	..	43	0
Parow, South Africa (June–August 2002) (Ijpma et al. 2004)	ARI	NPA; PCR	..	..	..	..	..	..	..	..
Khon Kaen, Thailand (April 2002–Aug 2004) (Teeratakulpisarn et al. 2007)	ALRI	NP secretion; PCR	..	..	..	..	..	..	..	..
KFSHRC, Riyadh, Saudi Arabia (July 2007–Nov 2008) (Al Hajjar et al. 2011)	ARI	NPA and BAL; PCR	1	0	1	0	7	28.6	9	22.2
Ankara, Turkey (Nov 2011–May 2012) (Azkur et al. 2014)	ALRI	NPS; PCR	..	..	..	..	..	..	..	..
Bamako, Mali (July 2011–Dec 2012) (Benet et al. 2015)	ALRI	..; PCR	..	..	..	..	..	..	12	0
Soweto, Gauteng, South Africa (Jan 2010–Dec 2013) (Cohen et al. 2016)	ALRI	NPA; PCR	147	0.7	..	..	..	..	..	..
Ho Chi Minh City, Vietnam (Nov 2004–Jan 2008) (Do et al. 2011a)	ARI	NS, TS, and NPA; PCR	..	..	..	..	..	..	20	0
Istanbul, Turkey (Oct 2006–March 2007) (Hatipoglu et al. 2011)	ALRI–Fever; ALRI	NPS; PCR	..	..	..	..	..	..	7	0
Amman, Jordan (Dec 2003–May 2004)(Kaplan et al. 2006)	ARI	NPA; PCR	..	..	..	..	..	..	8	0
Santa Maria (May 2005–May 2007) (Lozano C et al. 2009)	ALRI	NPA; PCR	..	..	..	..	..	..	24	0
Santa Rosa, Quetzaltenango, Guatemala (Nov 2007–Dec 2012) (McCracken et al. 2014)	ALRI	NPS and OPS; PCR	..	..	..	..	..	..	508	1.8

Location (reference)	Case definition	Specimen and test	0–5 m		6–11 m		12–59 m		0–59 m	
			Cases (No.)	hCFR (%)	Cases (No.)	hCFR (%)	Cases (No.)	hCFR (%)	Cases (No.)	hCFR (%)
Buenos Aires, Argentina (Nov–Dec 2009) (Pérez et al. 2012)†	ARI	NPA; IFA	..	..	..	..	..	..	..	..
Suzhou, China (Jan 2006–Dec 2007) (Wang et al. 2009)	ARI	respiratory specimens; PCR	..	..	..	..	..	..	..	..
Sousse area, Tunisia (Sep 2013–Dec 2014) (Brini et al. 2017)	ARI	NPA; PCR	..	..	..	..	..	..	60	8.3
Egypt, Jordan, Oman, Qatar and Yemen (Dec 2007–Feb 2014) (Horton et al. 2017a)	ARI	NPS and OPS; PCR	..	..	..	..	..	..	425	2.1
Manhica, Mozambique (Sep 2006–Sep 2007) (O'Callaghan-Gordo et al. 2011)	ALRI	NPA; PCR	..	..	..	..	..	..	29	10.3
Recife, Brazil (Apr 2008–Mar 2009) (Bezerra et al. 2011)	ARI	NPA; PCR	..	..	..	..	..	..	..	..
Cuangdong, China (June 2006–June 2007) (林创兴 et al. 2009)	ALRI	NP secretions, TS; PCR	..	..	..	..	..	..	..	..
Hunan Provincial People's Hospital, Changsha, China (Sep 2007–Aug 2008) (梁沫 et al. 2012)	ALRI	NPA; PCR	..	..	..	..	..	..	..	..
Suzhou, China (Jan 2009–Dec 2012) (邱秀娟 2015)	ARI	NPA; PCR	..	..	..	..	..	..	472	0
Suzhou, China (Jan 2006–Dec 2008) (骆亚丽 2009)	ARI	NPA; PCR	..	..	..	..	..	..	439	0
Shanghai, China (Dec 2006–Feb 2008) (沈军 2009)	ALRI	NPS; PCR	3	0	5	0	15	0	..	..
Rabat, Morocco (Nov 2010–Dec 2011) (Bassat and colleagues, unpublished)	ALRI	NPA; PCR	15	20	17	0	37	0	69	4.3
Taclobal, Philippines (May 2008–Feb 2015) (Oshitani and colleagues, unpublished)	ALRI	NPS; PCR	27	7.4	24	4.2	58	0	109	2.8
Muntinlupa, Philippines (Sep 2012–Feb 2015) (Oshitani and colleagues, unpublished)	ALRI	NPS; PCR	1	0	..	..	2	0	3	0
, Bangladesh (2010–2014) (Homaira and colleagues, unpublished)	ARI–Fever; ALRI	NS and TS; PCR	30	6.7	8	0	7	0	45	4.4
Nakhon Phanom, Thailand (Jan 2012–Dec 2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	NP/OP and induced sputum; PCR	..	..	..	..	..	..	2	0
Sa Kaeo, Thailand (Jan 2012–Dec 2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	NP/OP and induced sputum; PCR	1	0	..	..	1	0	2	0

† Among 13 hMPV-ALRI in infants <1 year, zero deaths were reported.

Location (reference)	Case definition	Specimen and test	0–5 m		6–11 m		12–59 m		0–59 m	
			Cases (No.)	hCFR (%)	Cases (No.)	hCFR (%)	Cases (No.)	hCFR (%)	Cases (No.)	hCFR (%)
Basse, Gambia (Nov 2011–Nov 2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	NPS, OPS, induced sputum specimens; PCR	72	0	73	1.4	74	1.4	219	0.9
Lusaka, Zambia (Oct 2011 – Oct 2014) (Deloria-Knoll and colleagues, unpublished)	ALRI	NPS, OPS, induced sputum specimens; PCR	22	9.1	19	10.5	12	0	53	7.5
Bamako, Mali (Jan 2012 – Jan 2014) (Deloria-Knoll and colleagues, unpublished)	ALRI	NPS, OPS, induced sputum specimens; PCR	16	0	14	0	18	5.6	48	2.1
Kilifi, Kenya (Aug 2011–Jul 2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	NPS, OPS, induced sputum specimens; PCR	18	5.6	16	0	22	4.5	56	3.6
Karachi, Pakistan (Aug 2009–Jul 2012) (Ali and colleagues, unpublished)	ARI	TS; PCR	32	3.1	24	0	28	0	84	1.2
Soweto, South Africa (Aug 2011–Aug 2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	NPS, OPS, induced sputum specimens; PCR	22	0	19	0	17	11.8	58	3.4
Matlab, Bangladesh (Jan 2012 – Dec 2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	NPS, OPS, induced sputum specimens; PCR	6	0	6	0	14	0	26	0
Dhaka, Bangladesh (Jan 2012–Dec 2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	NPS, OPS, induced sputum specimens; PCR	5	0	5	0	4	0	14	0
Kawayan and Caibiran, Philippines (Feb 2014–Jun 2016) (Oshitani and colleagues, unpublished)	ALRI	NPS; PCR	1	0	..	..	3	0	4	0
Paarl, South Africa (Jun 2012–Dec 2017) (Zar and colleagues, unpublished)	ALRI	NPS; PCR	9	0	6	0	5	0	20	0
Manhiça, Mozambique (Jan–Dec 2011) (Bassat and colleagues, unpublished)	ALRI	NPA; PCR	5	20	10	0	13	0	28	3.6
Concepcion, Chile (2012–2013) (Fasce and colleagues, unpublished)	ALRI	NPA; IFA	6	0	6	0	11	0	23	0
Pueto Princesa City, Philippines (Aug 2012–Feb 2015) (Oshitani and colleagues, unpublished)	ALRI	NPS; PCR	16	6.2	15	0	25	0	56	1.8
Kamalapur, Bangladesh (2013–2014) (Brooks and colleagues, unpublished)	ALRI	NPW; PCR	2	0	1	0	3	0	6	0

Location (reference)	Case definition	Specimen and test	0–5 m		6–11 m		12–59 m		0–59 m	
			Cases (No.)	hCFR (%)	Cases (No.)	hCFR (%)	Cases (No.)	hCFR (%)	Cases (No.)	hCFR (%)
Ciudad de Buenos Aires, Argentina (Jun 2008–Dec 2010) (Echavarria and colleagues, unpublished)	ARI	NPA; DFA	--	--	2	0	3	0	5	0
Multiple sites, Philippines (Jul 2000–Dec 2004) (Lucero and colleagues, unpublished)	ALRI	NPA and NPS; Viral culture	13	7.7	29	0	--	--	--	--
Soweto, Gauteng Prov, South Africa (2015–2017) (Nunes and colleagues, unpublished)	ALRI	NPS; PCR	63	0	58	0	30	0	151	0
Soweto, Gauteng, South Africa (Jan 2000–Dec 2002) (Madhi and colleagues, unpublished)	ALRI	NPA; PCR	22	4.5	34	0	70	1.4	126	1.6
Amman, Jordan (Mar 2010–Mar 2013) (Khuri-Bulos and colleagues, unpublished)	ALRI	NS and TS; PCR	101	1	68	0	--	--	--	--
Kilifi, Kenya (Jan 2007– Dec 2017) (Nokes and colleagues, unpublished)	ALRI	NPS; PCR	69	1.4	54	0	53	0	176	0.6
Buenos Aires, Argentina (May 2011–Aug 2013) (Polack and colleagues, unpublished)	ALRI	NPA; PCR	163	0.6	149	0.7	--	--	--	--
Klerksdorp, South Africa (2010–2015) (Cohen and colleagues, unpublished)	ALRI	NPA; PCR	19	5.3	11	0	18	0	50	2
Pietermaritzburg, Kwa–Zulu Natal Province, South Africa (2010–2015) (Cohen and colleagues, unpublished)	ALRI	NPA; PCR	41	2.4	29	0	41	0	111	0.9
Naval, Philippines (Sep 2012–Jul 2016) (Oshitani and colleagues, unpublished)	ALRI	NPS; PCR	12	0	8	0	21	0	41	0

Table A19–2e. hMPV – Description of included studies reporting proportions of hospitalised hMPV–ALRI cases in children under five years*†‡

Location (reference)	Case definition	Specimen and test	0–5 m		6–11 m		0–59 m	
			Tested ALRI (No.)	Proportion (%)	Tested ALRI (No.)	Proportion (%)	Tested ALRI (No.)	Proportion (%)
Montpellier, France (Nov 2003–Oct 2004) (Foulongne et al. 2006)	ARI	NPA; PCR	296	8.8	169	8.9	589	9.0
Liverpool, UK (Oct 2004–Oct 2005) (Hopkins et al. 2008)	ARI	NPA and non–bronchoscopic BAL; PCR	..	..	..	..	..	..
Reims, France (Oct 2007–Sep 2008) (Huguenin et al. 2012)	ALRI	NPA; PCR	..	..	..	..	..	..
Pisa, Italy (Jan 2000–May 2002) (Maggi et al. 2003)	ARI	NS; PCR	..	..	..	..	..	..
NVSN sites, USA (Oct 2001– Sep 2003)	ARI–Fever; Fever	NS and TS; PCR and culture	..	..	..	..	1104	3.8
Beersheba, Israel (Nov 2001–Oct 2005) (Wolf et al. 2010)	ALRI	NPW; PCR	..	..	..	..	997	8.0
Greece (Oct 1999–Sep 2000) (Xepapadaki et al. 2004)	ALRI	NPW; PCR	..	..	..	..	..	..
Milan, Italy (2004–2008) (Zappa et al. 2011)	ALRI	Pharyngeal swabs; PCR	144	9.0	36	8.3	..	..
Seoul, Korea (Sep 2011–Aug 2012) (Eem et al. 2014)	ARI	NPS; PCR	..	..	..	..	..	..

* ARI: acute respiratory infections requiring hospital admission. ALRI: physician diagnosed acute lower respiratory infections requiring hospital admission. ARI–Fever: hospitalised acute respiratory infections with fever. All: all diagnosis related to influenza (including influenza & pneumonia and other non-respiratory illnesses). NS: nasal swab. TS: throat swab. PCR: polymerase chain reaction. NPA: nasopharyngeal aspirate. NPS: nasopharyngeal swab. NPW: nasopharyngeal wash. NW: nasopharyngeal wash. OPS: oropharyngeal swab. BAL: bronchoalveolar lavage. IFA: indirect immunofluorescence assay. DFA: direct immunofluorescence assay. EIA: enzyme immunoassay.

† ..: Not available. Some included studies did not provide data for 0–5 m, 6–11 m, or 0–59 m while provided data for other age groups (e.g., 0–35 months).

‡ Proportion of hMPV in total ALRI cases that were tested.

Location (reference)	Case definition	Specimen and test	0–5 m		6–11 m		0–59 m	
			Tested ALRI (No.)	Proportion (%)	Tested ALRI (No.)	Proportion (%)	Tested ALRI (No.)	Proportion (%)
Tokyo, Japan (April 2007–March 2012) (Hamada et al. 2014)	ALRI	NS; PCR	--	--	--	--	--	--
Perth, Australia (Jan 2000–Dec 2005) (Moore et al. 2012)	ALRI	NPA; PCR	--	--	--	--	1179	13.7
Leganes, Madrid, Spain (Sep 2005–Aug 2008) (Calvo et al. 2010)	ALRI	NPA; PCR	--	--	--	--	--	--
Warsaw, Poland (Oct 2008–April 2011) (Pancer et al. 2014)	ARI	NPS; PCR and EIA	--	--	--	--	297	10.8
Cordoba, Spain (Jan–Dec 2011) (Rodriguez et al. 2016)	ARI	NPA; DFA	--	--	--	--	223	4.0
Melegnano, Italy (Oct 2004–Sep 2006) (Canducci et al. 2008)	ARI	NPA; PCR	--	--	--	--	--	--
Spain (Jan 2011–Jan 2013) (Cebey-López et al. 2015)	ALRI	NP sample; PCR	--	--	--	--	--	--
London, UK (2009–2012) (Cebey-López et al. 2015)	NA	NP sample; PCR	--	--	--	--	--	--
Nicosia, Cyprus (Nov 2010–Oct 2013) (Richter et al. 2016)	ARI	NS; PCR	--	--	--	--	--	--
Gipuzkoa, Spain; (July 2004–June 2007) (Cilla et al. 2009)	ARI; ARI–Fever	NPA; PCR and culture	386	10.1	153	13.1	--	--
Valencia Region, Spain (2014–2017) (Mira Iglesias and colleagues, unpublished)	All	NPS and NS; PCR	920	3.2	245	4.1	1929	2.9
Berlin, Germany (Jan 2010–Dec	ALRI	NPS; PCR	731	4.8	424	9.2	2516	7.2

Location (reference)	Case definition	Specimen and test	0–5 m		6–11 m		0–59 m	
			Tested ALRI (No.)	Proportion (%)	Tested ALRI (No.)	Proportion (%)	Tested ALRI (No.)	Proportion (%)
2014) (Rath and colleagues, unpublished)								
Aurora, Colorado, United States of America (2010–2016) (Simões and colleagues, unpublished)	ALRI	NW; PCR (and DFA)	2173	4.9	862	10.8	6424	9.8
São Paulo city, Brazil (March 2008–Feb 2010) (Durigon et al. 2015)	ARI	NPA; PCR	--	--	--	--	--	--
Aracaju´, Salvador, Recife, and Maceio, Brazil (April 2012–March 2013) (Gurgel et al. 2016)	ALRI	NPA; PCR	--	--	--	--	--	--
Sa Kaeo and Nakhon Phanom, Thailand (2005–2010) (Hasan et al. 2014)	ARI	NPS and serum specimens; PCR, serologic test and culture	397	2	--	--	3810	2.9
Lucknow, India (May 2011–April 2013) (Jain et al. 2014)	ALRI	NPA; PCR	--	--	--	--	235	5.1
Yaounde, Cameroon (Sep 2011–Sep 2013) (Kenmoe et al. 2016)	ARI–Fever	NPS; PCR	--	--	--	--	307	3.6
Sultan Qaboos University Hospital, Oman; (Dec 2007–Dec 2008) (Khamis et al. 2012)	ARI	NPA; PCR	--	--	--	--	518	1.2
Shandong, China (Jan 2011–Dec 2013) (Liu et al, 2015) (Liu et al. 2015)	ARI–Fever	TS; PCR	--	--	--	--	243	1.2
Beijing, China (July 2008–June 2010) (Lu et al. 2013)	ALRI	NPA; PCR	428	7	155	9.7	--	--

Location (reference)	Case definition	Specimen and test	0–5 m		6–11 m		0–59 m	
			Tested ALRI (No.)	Proportion (%)	Tested ALRI (No.)	Proportion (%)	Tested ALRI (No.)	Proportion (%)
Sao Paulo, Brazil (2003–2006) (Oliveira et al. 2009)	ARI	NPA and NS; PCR	..	..	..	..	1670	11.4
Yukon Kuskokwim Delta, USA (Oct 2005–Sep 2007) (Singleton et al. 2010)	ALRI	NP specimens; PCR	..	..	..	..	..	..
Arizona, Mexico (Oct 2010–Sep 2014) (Wansaula et al. 2016)	ARI–Fever; ALRI	NPS; PCR	..	..	..	..	17	11.8
Lanzou, China (Dec 2011–Nov 2012) (Yan et al. 2017)	ALRI	NPA; PCR	..	..	..	..	360	12.8
Ho Chi Minh City, Vietnam (May 2009–Dec 2010) (Do et al. 2016)	ARI	NPS; PCR	..	..	..	..	..	..
Lanzhou, China (Jan–Dec 2011) (Huang et al. 2013)	ARI	TS; PCR	..	..	..	..	..	..
Haryana, India (Aug 2009–July 2011) (Broor et al. 2014a)	All	NS and TS; PCR	..	..	..	..	245	1.2
Guangzhou, China (July 2009–June 2014) (Liao et al. 2015)	ARI	Pharyngeal swabs; PCR	..	..	..	..	..	..
Beijing, China (March 2010–Feb 2012) (Liu et al. 2013)	ARI	TS; PCR	..	..	..	..	..	..
Kolkata, India (April 2010–March 2011) (Mazumdar et al. 2013)	ALRI	NS and TS; PCR	..	..	..	..	108	0.9
Shantou, China (Jan–Dec 2007) (Ou et al. 2009)	ALRI	NPA; PCR	..	..	..	..	345	3.2
Hangzhou, China (Jan–Dec 2011) (Wang et al. 2013)	ALRI	NPA; DFA	..	..	..	..	..	..

Location (reference)	Case definition	Specimen and test	0–5 m		6–11 m		0–59 m	
			Tested ALRI (No.)	Proportion (%)	Tested ALRI (No.)	Proportion (%)	Tested ALRI (No.)	Proportion (%)
Changsha, China (Sep 2007–Aug 2008) (Xiao et al. 2012)	ALRI	NPA; PCR	350	6.6	320	7.8	1123	6.3
Beijing, China (Feb 2011–Jan 2012) (Zhang et al. 2015)	ALRI	Tracheal aspirate; PCR	--	--	--	--	--	--
Dhaka, Bangladesh (Aug 2014–Jul 2015) (Bhuyan et al. 2017)	ARI	NS; PCR	--	--	--	--	200	13
Sulaimani, Iraq (Apr 2011–Mar 2012) (TAG 2015)	ARI	NPS and TS; --	--	--	--	--	300	16
Manhica, Mozambique (Sep 2006–Sep 2007) (O'Callaghan-Gordo et al. 2011)	ALRI	NPA; PCR	--	--	--	--	807	4.8
Asembo, Kenya (Mar 2007–Feb 2008) (Feikin et al. 2013)	ALRI	NPS or OPS; PCR	--	--	--	--	350	4.9
Chongqing, China (April 2006–March 2008) (Chen et al. 2010)	ALRI	NPA; PCR	428	27.8	--	--	--	--
Recife, Brazil (Apr 2008–Mar 2009) (Bezerra et al, 2011)	ARI	NPA; PCR	--	--	--	--	211	9.5
Cape Town, South Africa (2003–2004) (Smuts 2008)	ARI	NPA, tracheal aspirate, BAL; PCR	--	--	--	--	1055	2.7
Guangdong, China (Mar 2010–Feb 2011) (Xu et al. 2012)	ARI	TS; PCR	--	--	--	--	--	--
Changsha, China (Apr 2012–Mar 2013) (彭颖 2014)	ALRI	NPA; PCR	143	13.3	159	20.8	595	17.1
Chongqing, China (Apr 2008–Mar 2009) (杜丽娜 2010)	ARI	NPA; PCR	--	--	--	--	--	--

Location (reference)	Case definition	Specimen and test	0–5 m		6–11 m		0–59 m	
			Tested ALRI (No.)	Proportion (%)	Tested ALRI (No.)	Proportion (%)	Tested ALRI (No.)	Proportion (%)
Yanting, China (Jan 2011–Dec 2012) (何杨 2015)	ARI	NPA; PCR	..	..	..	..	..	..
Suzhou, China (Nov 2005–Oct 2006) (王宇清 2007)	ARI	NPA; PCR	590	5.3	399	7.8	1729	7.1
Jiaxing, China (Jan–Dec 2010) (盛曙君 2013)	ARI	NPA; DFA	2153	2.1	690	1.6	..	..
Suzhou, China (Jan 2009–Dec 2012) (邱秀娟 2015)	ARI	NPA; PCR	3024	4.7	2792	4.8	9949	4.7
Beijing, China (Oct 2010–Sep 2012) (魏美晨 2013)	ARI	NP specimens; PCR	28	3.6	25	16	..	..
Chenzhou, China (Jul 2013–Jun 2014) (吴琼 et al. 2017)	ARI–Fever	NS; PCR	..	..	..	..	489	5.3
Wenzhou, China (Jan–Dec 2014) (张海邻 et al. 2017)	ALRI	NPA; DFA	..	..	..	..	922	3.4
Guangzhou, China (Jan–Dec 2015) (蔡勇 et al. 2017)	ARI	NPS; PCR	216	0.9	310	5.8	..	..
Yinchuan, China (Oct 2011–Sep 2012)(张俊华 et al. 2013)	ARI	NPS; DFA	103	12.6	152	9.9	..	..
Baiyin, China (Jul 2012–Jul 2013) (于德山 et al. 2017)	ALRI	NPA; PCR	20	15.0	93	9.7	391	13.0
Shijiazhuang, China (Mar 2015–Feb 2016) (王胜娥 2016)	ALRI	BAL; PCR	..	..	..	..	351	3.4
Changsha, China (Mar 2010–Feb 2011) (赵辛 2012)	ALRI	NPA; PCR	171	4.1	173	6.9	707	4.1

Location (reference)	Case definition	Specimen and test	0–5 m		6–11 m		0–59 m	
			Tested ALRI (No.)	Proportion (%)	Tested ALRI (No.)	Proportion (%)	Tested ALRI (No.)	Proportion (%)
Changsha, China (Apr 2013–Mar 2014) (刘沁 et al. 2015)	ALRI	NPA; PCR	138	5.8	142	6.3	442	6.8
Chongqing, China (Jun 2009–May 2012) (卢庆彬 2013)	ARI	NPA; PCR	1028	2.6	505	5.1	2272	3.4
Suzhou, China (Jan 2006–Dec 2008) (季伟 et al. 2010)	ARI	NPA; PCR	1682	7.5	1468	9.9	5774	9.6
Hangzhou, China (Jan 2011–Dec 2013) (季伟 et al. 2010)	ALRI	NPA; PCR	..	..	..	..	..	..
Suzhou, China (July 2007–June 2008) (季伟 et al. 2010)	ARI	NPA; PCR	563	9.9	507	10.3	..	..
Rabat, Morocco (Nov 2010–Dec 2011) (Bassat and colleagues, unpublished)	ALRI	NPA; PCR	100	15	112	15.2	631	10.9
Taclobal, Philippines (May 2008–Feb 2015) (Oshitani and colleagues, unpublished)	ALRI	NPS; PCR	816	3.1	510	4.5	2420	4.2
Muntinlupa, Philippines (Sep 2012–Feb 2015) (Oshitani and colleagues, unpublished)	ALRI	NPS; PCR	70	1.4	59	0	188	1.1
, Bangladesh (2010–2014) (Homaira and colleagues, unpublished)	ARI–Fever; ALRI	NS and TS; PCR	451	6.7	198	4	831	5.4
Nakhon Phanom, Thailand (Jan 2012–Dec 2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	NP/OP and induced sputum; PCR	5	0	6	0	44	2.3

Location (reference)	Case definition	Specimen and test	0–5 m		6–11 m		0–59 m	
			Tested ALRI (No.)	Proportion (%)	Tested ALRI (No.)	Proportion (%)	Tested ALRI (No.)	Proportion (%)
Sa Kaeo, Thailand (Jan 2012–Dec 2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	NP/OP and induced sputum; PCR	7	14.3	11	0	51	3.9
Tehran, Iran (Islamic Republic of) (Mar 2010– Mar 2013) (Vahid and colleagues, unpublished)	ALRI	NPS and TS; PCR	78	1.3	26	7.7	158	5.7
Lusaka, Zambia (Oct 2011 – Oct 2014) (Deloria-Knoll and colleagues, unpublished)	ALRI	NPS, OPS, induced sputum specimens; PCR	314	7	143	13.3	590	9
Bamako, Mali (Jan 2012 – Jan 2014) (Deloria-Knoll and colleagues, unpublished)	ALRI	NPS, OPS, induced sputum specimens; PCR	297	5.4	151	9.3	659	7.3
Kilifi, Kenya (Aug 2011–Jul 2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	NPS, OPS, induced sputum specimens; PCR	185	9.7	116	13.8	566	9.9
Karachi, Pakistan (Aug 2009–Jul 2012) (Ali and colleagues, unpublished)	ARI	TS; PCR	372	8.6	295	8.1	1150	7.3
Soweto, South Africa (Aug 2011–Aug 2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	NPS, OPS, induced sputum specimens; PCR	431	5.1	212	9	866	6.7
Matlab, Bangladesh (Jan 2012 – Dec 2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	NPS, OPS, induced sputum specimens; PCR	94	6.4	74	8.1	327	8
Dhaka, Bangladesh (Jan 2012–Dec 2013) (Deloria-	ALRI	NPS, OPS, induced sputum specimens; PCR	42	11.9	47	10.6	198	7.1

Location (reference)	Case definition	Specimen and test	0–5 m		6–11 m		0–59 m	
			Tested ALRI (No.)	Proportion (%)	Tested ALRI (No.)	Proportion (%)	Tested ALRI (No.)	Proportion (%)
Knoll and colleagues, unpublished)								
Kawayan and Caibiran, Philippines (Feb 2014–Jun 2016) (Oshitani and colleagues, unpublished)	ALRI	NPS; PCR	39	2.6	28	0	123	3.3
Nha Trang city, Viet Nam (Jan 2007–Dec 2014) (Yoshida and colleagues, unpublished)	ALRI	NPS; PCR	255	2.4	241	3.3	1300	4.9
Paarl, South Africa (Jun 2012–Dec 2017) (Zar and colleagues, unpublished)	ALRI	NPS; PCR	102	8.8	42	14.3	201	10
Manhiça, Mozambique (Jan–Dec 2011) (Bassat and colleagues, unpublished)	ALRI	NPA; PCR	114	4.4	96	10.4	413	6.3
Concepcion, Chile (2012–2013) (Fasce and colleagues, unpublished)	ALRI	NPA; IFA	216	2.8	85	7.1	464	5
Pueto Princesa City, Philippines (Aug 2012–Feb 2015) (Oshitani and colleagues, unpublished)	ALRI	NPS; PCR	236	3.4	166	6	694	5
Kamalapur, Bangladesh (2013–2014) (Brooks colleagues, unpublished)	ALRI	NPW; PCR	19	10.5	16	6.2	67	9
Ciudad de Buenos Aires, Argentina (Jun 2008–Dec 2010) (Echavarria and colleagues, unpublished)	ARI	NPA; DFA	12	0	18	5.6	73	2.7

Location (reference)	Case definition	Specimen and test	0–5 m		6–11 m		0–59 m	
			Tested ALRI (No.)	Proportion (%)	Tested ALRI (No.)	Proportion (%)	Tested ALRI (No.)	Proportion (%)
Multiple sites, Philippines (Jul 2000–Dec 2004) (Lucero and colleagues, unpublished)	ALRI	NPA and NPS; Viral culture	233	5.6	278	10.4	..	..
Soweto, Gauteng Prov, South Africa (2015–2017) (Nunes and colleagues, unpublished)	ALRI	NPS; PCR	2461	2.6	1185	4.9	4400	3.4
Soweto, Gauteng, South Africa (Jan 2000–Dec 2002) (Madhi and colleagues, unpublished)	ALRI	NPA; PCR	326	6.7	301	11.3	1409	8.9
Pune, India (May 2009–Apr 2013) (Hirve and colleagues, unpublished)	ALRI	NPS; PCR	6	33.3	17	11.8	76	19.7
Amman, Jordan (Mar 2010–Mar 2013) (Khuri-Bulos and colleagues, unpublished)	ALRI	NS and TS; PCR	1017	9.1	497	12.1	..	..
Kilifi, Kenya (Jan 2007– Dec 2017) (Nokes and colleagues, unpublished)	ALRI	NPS; PCR	1347	5.1	760	7.1	3372	5.2
Buenos Aires, Argentina (May 2011–Aug 2013) (Polack and colleagues, unpublished)	ALRI	NPA; PCR	1794	9.1	956	15.6	..	..
Kathmandu and surrouning disctricts, Nepal (Jan 2006–Jan 2008) (Strand and colleagues, unpublished)	ALRI	NPA; PCR	248	2.4	173	1.2	..	..
Klerksdorp, South Africa	ALRI	NPA; PCR	504	3.8	269	4.1	1259	4

Location (reference)	Case definition	Specimen and test	0–5 m		6–11 m		0–59 m	
			Tested ALRI (No.)	Proportion (%)	Tested ALRI (No.)	Proportion (%)	Tested ALRI (No.)	Proportion (%)
(2010–2015) (Cohen and colleagues, unpublished)								
Pietermaritzburg, Kwa–Zulu Natal Province, South Africa (2010–2015) (Cohen and colleagues, unpublished)	ALRI	NPA; PCR	883	4.6	442	6.6	2164	5.1
Naval, Philippines (Sep 2012–Jul 2016) (Oshitani and colleagues, unpublished)	ALRI	NPS; PCR	451	2.4	218	2.8	1092	2.9

Table A19–2f. hMPV – Description of included studies reporting hospitalisation rates of hMPV–ALRI with hypoxaemia (per 1,000 children per year).*

Location (reference)	Case Definition	Denominator type	Specimen and test	0–5 m	6–11 m	12–23 m	24–59 m	0–59 m
Nakhon Phanom, Thailand (Jan 2012–Dec 2013) (Deloria-Knoll and colleagues, unpublished)	ALRI AND hypoxaemia OR danger signs	Census derived population	NP/OP and induced sputum; PCR	--	--	0	0	0
Sa Kaeo, Thailand (Jan 2012–Dec 2013) (Deloria-Knoll and colleagues, unpublished)	ALRI AND hypoxaemia OR danger signs	Census derived population	NP/OP and induced sputum; PCR	--	--	0	0.1	0.1
Kawayan and Caibiran, Philippines (Feb 2014–Jun 2016) (Oshitani and colleagues, unpublished)	ALRI AND hypoxaemia OR danger signs	Defined population estimates	NPS; PCR	0	0	1	0	0.2
Nha Trang city, Viet Nam (Jan 2007–Dec 2014) (Yoshida and colleagues, unpublished)	ALRI AND hypoxaemia OR danger signs	Census derived population	NPS; PCR	--	--	0.3	0.1	0.2
Paarl, South Africa (Jun 2012–Dec 2017) (Zar and colleagues, unpublished)	ALRI AND hypoxaemia OR ICU OR MV	Defined population estimates	NPS; PCR	6	0	0	0	0.8
Manhiça, Mozambique (Jan–Dec 2011) (Bassat and colleagues, unpublished)	ALRI AND hypoxaemia OR danger signs	Census derived population	NPA; PCR	0	0.4	0	0.1	0.1
Kamalapur, Bangladesh (2013–2014) (Brooks colleagues, unpublished)	ALRI AND hypoxaemia OR danger signs	Defined population estimates	NPW; PCR	0.8	0	0	0	0.3
Multiple sites, Philippines (Jul 2000–Dec 2004) (Lucero and colleagues, unpublished)	ALRI AND hypoxaemia OR danger signs	Defined population estimates	NPA and NPS; Viral culture	1.7	2.2	1.3	--	--
Soweto, Gauteng, South Africa (Jan 2000–Dec 2002) (Madhi and colleagues, unpublished)	ALRI AND hypoxaemia OR ICU OR danger signs	Defined population estimates	NPA; PCR	2.2	1.1	0.7	0.3	0.6
Amman, Jordan (Mar 2010–Mar 2013) (Khuri-Bulos and colleagues, unpublished)	ALRI AND hypoxaemia OR ICU OR MV	Census derived population	NS and TS; PCR	0.3	0.1	0	--	--

* ALRI: physician diagnosed acute lower respiratory infections requiring hospital admission. ICU: intensive care unit. MV: mechanical ventilation. All: all diagnosis related to influenza (including influenza & pneumonia and other non-respiratory illnesses). NP specimens: nasopharyngeal specimens. OP specimens: oropharyngeal specimens. NS: nasal swab. TS: throat swab. NPA: nasopharyngeal aspirate. NPS: nasopharyngeal swab. PCR: polymerase chain reaction.

Location (reference)	Case Definition	Denominator type	Specimen and test	0–5 m	6–11 m	12–23 m	24–59 m	0–59 m
Kilifi, Kenya (Jan 2007– Dec 2017) (Nokes and colleagues, unpublished)	ALRI AND hypoxaemia OR ICU OR danger signs	Census derived population	NPS; PCR	1.5	1.3	0.3	0.1	0.4
Valencia Region, Spain (2014–2017) (Mira Iglesias and colleagues, unpublished)	All AND hypoxaemia OR ICU OR MV	Census derived population	NPS and NS; PCR	--	--	0	0	0
Buenos Aires, Argentina (May 2011–Aug 2013) (Polack and colleagues, unpublished)	ALRI AND hypoxaemia OR ICU OR MV	Census derived population	NPA; PCR	1.1	1	0.2	--	--

Table A19–3a. hPIV – Description of included studies reporting incidence rates of hPIV–ALRI cases (per 1,000 children per year) in children under five years*

Location (reference)	Case Definition	Denominator type	Specimen and test	0–5 m	6–11 m	12–23 m	24–59 m	0–59 m
Ballabgarh, India (2001–2005) (Broor et al. 2007)	ALRI	Defined population base	NPA; DFA	..	..	80.4	..	..
Navajo and White Mountain Apache, USA (2009) (Bhat et al. 2013)	ALRI	Defined population base	Nasal wash; PCR	..	..	..	..	..
Faridabad, India (Aug 2012–Aug 2014) (Krishnan and colleagues, unpublished)	ALRI	Census derived estimate	OP and nasal specimens; PCR	45.5	90	46.2	11.9	29.4
Oshikhandass, Pakistan (Dec 2012–Dec 2013) (Rasmussen and colleagues, unpublished)	ALRI	Defined population base	NPS; PCR	0	15.9	46.2	9.2	17.3
Kamalapur, Bangladesh (2013–2014) (Brooks and colleagues, unpublished)	ALRI	Defined population base	NPW; PCR	11.5	59.8	92.1	45.2	39.5
Paarl, South Africa (Jun 2012–Dec 2017) (Zar and colleagues, unpublished)	ALRI	Defined population base	NPS; PCR	91.6	70.4	52.8	18	43.1
Bhaktapur, Nepal (2004–2007) (Strand and colleagues, unpublished)	ALRI	Defined population base	NPA; PCR	64.3	81.4	53.6	..	..
Nashville, USA (1976–2001) (Williams et al. 2004)	ALRI; croup	Defined population base	NW; Culture	..	..	..	..	18.8
Mirzapur, Bangladesh (1993–1994) ('The importance of viral infection in pneumonia among children under age 2 years' 2006)	ALRI	Defined population base	NPA; ELISA	..	..	..	..	..
Brisbane, Australia (2010–2014) (Sarna et al. 2018)	ALRI	Defined population base	NS; PCR	..	..	..	..	..
Perth, Australia (1996–1999) (Kusel et al. 2006)	ALRI	Defined population base	NPA; PCR	..	..	..	..	..

* ALRI: acute lower respiratory infections according to 2005 WHO IMCI. NP specimens: nasopharyngeal specimens. OP specimens: oropharyngeal specimens. NS: nasal swab. TS: throat swab. NPA: nasopharyngeal aspirate. NPS: nasopharyngeal swab. NPW: nasopharyngeal wash. NW: nasal wash. IFA: indirect immunofluorescence assay. DFA: direct immunofluorescence assay. PCR: polymerase chain reaction.

Barcelona, Spain (1996–1999) (Puig et al. 2008)	ALRI; croup	Defined population base	NPA; Culture with IFA	..	..	..	..	..

Table A19–3b. hPIV – Description of included studies reporting incidence rates of hPIV–severe ALRI cases (per 1,000 children per year) in children younger than five years*

Location (reference)	Case Definition	Denominator type	Specimen and test	0–5 m	6–11 m	12–23 m	24–59 m	0–59 m
Karachi, Pakistan (2011–2014) (Ali et al. 2016)	sALRI	Defined population base	NPS; PCR	72.7	..	..	..	..
Ballabgarh, India (2001–2005) (Broor et al. 2007)	sALRI	Defined population base	NPA; DFA	..	..	8.7	..	..
Faridabad, India (Aug 2012–Aug 2014) (Krishnan and colleagues, unpublished)	sALRI	Census derived estimate	OP and nasal specimens; PCR	25.3	58.8	29.7	9.1	19.6
Kamalapur, Bangladesh (2013–2014) (Brooks and colleagues, unpublished)	sALRI	Defined population base	NPW; PCR	0.6	5.4	0	2.2	1.6
Paarl, South Africa (Jun 2012–Dec 2017) (Zar and colleagues, unpublished)	sALRI	Defined population base	NPS; PCR	76.9	58	29.9	10.2	30.4

* sALRI: severe acute lower respiratory infections (with chest wall indrawing and danger signs) according to 2005 WHO IMCI. OP specimens: oropharyngeal specimens. NPA: nasopharyngeal aspirate. NPS: nasopharyngeal swab. NPW: nasopharyngeal wash. DFA: direct immunofluorescence assay. PCR: polymerase chain reaction.

Table A19–3c. hPIV – Description of included studies reporting hospitalisation rates of hPIV–ALRI cases (per 1,000 children per year) in children under five years*

Location (reference)	Case Definition	Denominator type	Specimen and test	0–5 m	6–11 m	12–23 m	24–59 m	0–59 m
Sa Kaeo and Nakhon Phanom, Thailand (2005–2010) (Hasan et al. 2014)	ARI	Census derived estimate	NPS and serum specimens; PCR, serologic test and culture	3.6	--	--	3.2	5.5
Memphis, Nashville, and Salt Lake City (EPIC), USA (2010–2012) (Jain et al. 2015)	ALRI	Census derived estimate	NPS and OPS; PCR and serologic testing	--	--	--	0.2	0.2
Iqaluit, Nunavut (1997–1998) (Banerji et al. 2001)	ALRI	Census derived estimate	NPA; IFA	8.9	--	--	--	--
NVSN sites, USA (2000–2004) (Weinberg et al. 2009)	Fever; ARI	Census derived estimate	NS and TS; PCR	3	1.7	1.5	0.4	1
Haryana, India (2009–2011) (Broor et al. 2014b)	All	Census derived estimate	NS and TS; PCR	--	--	--	--	0.7
Kakuma and Dadaab, Kenya (2007–2010) (Ahmed et al. 2012)	ALRI	Census derived estimate	NPS and OPS; PCR	--	--	--	--	6.2
Kiel, Germany (1996–2000) (Weigl et al. 2005)	ALRI; croup	Census derived estimate	NPA; PCR	--	--	--	--	0.5
Navajo and White Mountain Apache, USA (2009) (Bhat et al. 2013)	ALRI	Defined population base	NW; PCR	--	--	--	--	--
PYNEH and QMH, Hong Kong (2003–2006) (Chiu et al. 2010)	ARI–Fever	Census derived estimate	NPA; DFA and culture	10.8	7.2	9.9	4.8	6.6
Gipuzkoa, Spain (2004–2007) (Cilla et al. 2009)	ARI; ARI–Fever	Census derived estimate	NPA; PCR and culture	4	3.2	1.2	--	--
Kawayan and Caibiran, Philippines (2014–2016) (Oshitani and colleagues, unpublished	ALRI	Defined population base	NPS; PCR	9.1	10.9	0	1.2	2.4
Kilifi, Kenya (2007–2017) (Nokes and colleagues, unpublished)	ALRI	Census derived estimate	NPS; PCR	5	3.9	1.6	0.4	1.5
Nha Trang city, Viet Nam (2007–2016) (Yoshida and colleagues, unpublished)	ALRI	Census derived estimate	NPS; PCR	--	--	1.6	0.2	0.8

* ARI: acute respiratory infections requiring hospital admission. ALRI: physician diagnosed acute lower respiratory infections requiring hospital admission. ARI–Fever: hospitalised acute respiratory infections with fever. All: all diagnosis related to influenza (including influenza & pneumonia and other non-respiratory illnesses). NS: nasal swab. TS: throat swab. NW: nasal wash. PCR: polymerase chain reaction. NPA: nasopharyngeal aspirate. NPS: nasopharyngeal swab. OPS: oropharyngeal swab. NPW: nasopharyngeal wash. IFA: indirect immunofluorescence assay. DFA: direct immunofluorescence assay. IF: immunofluorescence.

Location (reference)	Case Definition	Denominator type	Specimen and test	0–5 m	6–11 m	12–23 m	24–59 m	0–59 m
Buenos Aires, Argentina (Jun 2008–Dec 2010) (Echavarria and colleagues, unpublished)	ARI	Defined population base	NPA; IFA	3	1	--	--	2.2
multiple areas, Philippines (Jul 2000–Dec 2004) (Lucero and colleagues, unpublished)	ALRI	Defined population base	Blood, NPS and NPA; Serum and culture	11.9	7.8	2.3	--	--
Amman, Jordan (Mar 2010–Mar 2013) (Khuri-Bulos and colleagues, unpublished)	ALRI	Census derived estimate	NS and TS; PCR	0.7	0.5	0.3	--	--
Basse, Gambia (2012–2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	Census derived estimate	NPS/OPS, Induced Sputum; PCR	7.6	5.8	1.6	0.5	2
Nakhon Phanom, Thailand (Jan 2012–Dec 2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	Census derived estimate	NP/OP and induced sputum; PCR	--	--	0.3	0.1	0.3
Sa Kaeo, Thailand (Jan 2012–Dec 2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	Census derived estimate	NP/OP and induced sputum; PCR	--	--	0.7	0.1	0.5
Buenos Aires, Argentina (2000–2017) (Gentile and colleagues, unpublished)	ALRI	Defined population base	NPA; IFA	--	--	3.5	1.1	4.4
Manhiça, Mozambique (Jan 2011–Jul 2014) (Bassat and colleagues, unpublished)	ALRI	Defined population base	NPA; PCR	3.5	2.3	0.8	0.2	0.9
Iquique, Chile (2012–2013) (Fasce and colleagues, unpublished)	ALRI	Censue derived estimate	NPA; IF	--	--	1	0.2	0.7
Concepcion, Chile (2012–2013) (Fasce and colleagues, unpublished)	ALRI	Censue derived estimate	NPA; IF	--	--	0.4	0.2	0.4
Soweto, South Africa (Mar 1998–Oct 2005) (Madhi and colleagues, unpublished)	ALRI	Defined population base	NPA; IFA	5	3.3	0.9	0.1	1
Kamalapur, Bangladesh (2013–2014) (Brooks and colleagues, unpublished)	ALRI	Defined population base	NPW; PCR	0.8	3.8	0	0	0.9
Paarl, South Africa (Jun 2012–Dec 2017) (Zar and colleagues, unpublished)	ALRI	Defined population base	NPS; PCR	26.1	16.3	4.2	3.1	8.5
Klerksdorp, South Africa (2010–2015) (Cohen and colleagues, unpublished)	ALRI	Census derived estimate	NPA; PCR	3.4	2.8	1.4	0.3	1.1
Pietermaritzburg, South Africa (2010–2015) (Cohen and colleagues, unpublished)	ALRI	Census derived estimate	NPA; PCR	3.2	2.3	0.9	0.2	0.9
Hamburg, Dresden, Freiburg, Bochum, Germany (1999–2001) (Forster et al. 2004)	ALRI; croup	Defined population base	NP secretion; PCR	--	--	--	--	--

Location (reference)	Case Definition	Denominator type	Specimen and test	0–5 m	6–11 m	12–23 m	24–59 m	0–59 m
Suzhou, China (2007–2008) (Ji et al. 2010)	ALRI	Census derived estimate	nasal aspirate; DFA	--	--	--	--	0.6
Sioux Lookout, Ontario, Canada (2007–2012) (McCuskee et al. 2014)	ALRI	Census derived estimate	--; immunochromatography assay and culture (all tested by culture)	--	--	--	--	--
Severo Ochoa Hospital, Madrid, Spain (2011–2012) (Olabarrieta et al. 2015)	ALRI	Defined population base	NPA; PCR	--	--	--	--	--
Manhica, Mozambique (2006–2007) (O'Callaghan-Gordo et al. 2011)	ALRI	Census derived estimate	NPA; PCR	--	--	--	--	1.5
Asembo, Kenya (2007–2010) (Feikin et al. 2013)	ALRI	Census derived estimate	NPS or OPS; PCR	--	--	--	--	30
multiple areas, Bangladesh (2010–2014) (Homaira and colleagues, unpublished)	ARI–Fever; ALRI	Census derived estimate	NS and TS; PCR	--	--	--	--	1.4

Table A19–3d. hPIV – Description of included studies reporting hCFRs (%) of hPIV–ALRI cases in children younger than five years*†

Location (reference)	Case definition	Specimen and test	0 –5 m		6–11 m		12–59 m		0–59 m	
			Cases (No.)	hCFR (%)	Cases (No.)	hCFR (%)	Cases (No.)	hCFR (%)	Cases (No.)	hCFR (%)
São Paulo city, Brazil (2008–2010) (Durigon et al. 2015)	ARI	NPA; PCR	..	..	..	..	..	..	..	..
Takeo Province and Kampong Cham Province, Cambodia (2007–2010) (Guerrier et al. 2013)	ALRI	NPA; PCR	..	..	..	..	..	..	51	0
Sa kaeo, Nakhon Phanom, Thailand (2003–2007) (Morgan et al. 2013)	ARI	NPS and serum specimen; PCR, serologic test and culture	..	..	..	..	..	..	370	0
São Paulo city, Brazil (2005–2007) (Pecchini et al. 2015)	ARI–Fever; ARI	NP secretion; IFA	..	..	..	..	..	..	45	8.9
Yukon Kuskokwim Delta, USA (2005–2007) (Singleton et al. 2010)v	ALRI	NP specimens; PCR	..	..	..	..	..	..	..	..
Santiago, Chile (2001–2004) (Vega-Briceño et al. 2007)	ALRI	NPS; DFA	..	..	..	..	..	..	..	..
Pune, India (2002–2004) (Yeolekar et al. 2008)	ARI	NPA; IFA	..	..	..	..	..	..	..	..
Bamako, Mali (2011–2012) (Benet et al. 2015)	ALRI	NS; PCR	..	..	..	..	..	..	13	15.4
multi sites, South Africa (2009–2014) (Cohen et al. 2015)	ALRI	NPA; PCR	..	..	..	..	..	..	952	1.6
multi sites, South Africa (2010–2013) (Cohen et al. 2016)	ALRI	NPA; PCR	226	2.7	..	..	..	..	..	..
Ho Chi Minh City, Vietnam (2004–2008) (Do et al. 2011b)	ARI	NS, TS, and NPA; PCR	..	..	..	..	..	..	19	0
Ho Chi Minh City, Vietnam (2009–2010) (Do et al. 2016)	ARI	NPS; PCR	..	..	..	..	..	..	..	..

* ARI: hospitalised acute respiratory infections. ALRI: physician diagnosed acute lower respiratory infections requiring hospital admission. ARI–Fever: hospitalised acute respiratory infections with fever. NS: nasal swab. TS: throat swab. NW: nasal wash. PCR: polymerase chain reaction. NPA: nasopharyngeal aspirate. NPS: nasopharyngeal swab. OPS: oropharyngeal swab. NPW: nasopharyngeal wash. IFA: indirect immunofluorescence assay. DFA: direct immunofluorescence assay. IF: immunofluorescence.

† ..: not available. Some included studies did not provide data for 0 –5 m, 6–11 m , 12–59 m, or 0–59 m while provided data for other age groups (e.g., 0–23 m).

Location (reference)	Case definition	Specimen and test	0 –5 m		6–11 m		12–59 m		0–59 m	
			Cases (No.)	hCFR (%)	Cases (No.)	hCFR (%)	Cases (No.)	hCFR (%)	Cases (No.)	hCFR (%)
Madrid, Spain (1994–2000) (García García et al. 2001)	ALRI; croup	NP secretions; IFA	--	--	--	--	--	--	--	--
Istanbul, Turkey (2006–2007) (Hatipoglu et al. 2011)	ALRI–Fever; ALRI	NPS; DFA	--	--	--	--	--	--	15	0
Haryana, India (2009–2011) (Broor et al. 2014b)	All	NS and TS; PCR	--	--	--	--	--	--	10	0
multiple sites, Korea (1994–1998) (Kim et al. 2011)	ALRI; croup	NPA; IFA	--	--	--	--	--	--	--	--
Bueno Aires, Cordoba, Santa Fe, Mar del Plata, Argentina (1993–1994) (Carballal et al. 2001)	ALRI	NPA; DFA	--	--	--	--	--	--	27	0
Sousse area, Tunisia (2013–2014) (Brini et al. 2017)	ARI	NPA; PCR	--	--	--	--	--	--	44	15.9
Egypt (2007–2014) (Horton et al. 2017a)	ARI	NPS and OPS; PCR	--	--	--	--	151	1.3	335	3.6
Jordan (2008–2010) (Horton et al. 2017a)	ARI	NPS and OPS; PCR	--	--	--	--	25	0	58	1.7
Oman (2008–2009) (Horton et al. 2017a)	ARI	NPS and OPS; PCR	--	--	--	--	23	0	40	0
Qatar (2008–2009) (Horton et al. 2017a)	ARI	NPS and OPS; PCR	--	--	--	--	1	0	2	0
Yemen (2010–2014) (Horton et al. 2017a)	ARI	NPS and OPS; PCR	--	--	--	--	21	0	64	1.6
Manhica, Mozambique (2006–2007) (O'Callaghan-Gordo et al. 2011)	ALRI	NPA; PCR	--	--	--	--	--	--	31	3.2
PYNEH and QMH, Hong Kong (2003–2006) (Chiu et al. 2010)	ARI–Fever	NPA; DFA and culture	--	--	--	--	--	--	74	0
Kunming, China (2009–2010) (郑文静 2011)	ARI	NPS; PCR	--	--	--	--	--	--	102	0
Kawayan and Caibiran, Philippines (2014–2016) (Oshitani and colleagues, unpublished	ALRI	NPS; PCR	3	0	5	0	4	0	12	0
Naval, Philippines (Sep 2012–Jul 2016) (Oshitani and colleagues, unpublished)	ALRI	NPS; PCR	22	0	21	0	30	0	73	0
Muntinlupa, Philippines (Sep 2012–Feb 2015) (Oshitani and colleagues, unpublished)	ALRI	NPS; PCR	1	100	1	0	1	0	3	33.3
Ospital ng Palawan, Philippines (Aug 2012–Feb 2015) (Oshitani and colleagues, unpublished)	ALRI	NPS; PCR	8	0	5	0	20	5	33	3

Location (reference)	Case definition	Specimen and test	0 –5 m		6–11 m		12–59 m		0–59 m	
			Cases (No.)	hCFR (%)	Cases (No.)	hCFR (%)	Cases (No.)	hCFR (%)	Cases (No.)	hCFR (%)
Kilifi, Kenya (2007–2017) (Nokes and colleagues, unpublished)	ALRI	NPS; PCR	84	2.4	50	2	67	4.5	201	3
Buenos Aires, Argentina (Jun 2008–Dec 2010) (Echavarria and colleagues, unpublished)	ARI	NPA; IFA	3	0	2	0	6	0	11	0
multiple areas, Philippines (Jul 2000–Dec 2004) (Lucero and colleagues, unpublished)	ALRI	Blood, NPS and NPA; Serum and culture	35	2.9	35	0	..	..	..	..
Amman, Jordan (Mar 2010–Mar 2013) (Khuri-Bulos and colleagues, unpublished)	ALRI	Nasal and throat swabs; PCR	45	0	31	0	..	..	..	..
multiple areas, Bangladesh (2010–2014) (Homaira and colleagues, unpublished)	ARI–Fever; ALRI	Nasal and throat swabs; PCR	27	0	16	0	15	0	58	0
Matlab, Bangladesh (Jan 2012 – Dec 2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	NPS/OPS, Induced Sputum; PCR	9	0	8	0	25	0	42	0
Basse, Gambia (2012–2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	NPS/OPS, Induced Sputum; PCR	50	2	43	2.3	39	2.6	132	2.3
Lusaka, Zambia (Oct 2011 – Oct 2014) (Deloria-Knoll and colleagues, unpublished)	ALRI	NPS/OPS, Induced Sputum; PCR	26	7.7	24	12.5	17	11.8	67	10.4
Nakhon Phanom, Thailand (Jan 2012–Dec 2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	NP/OP and induced sputum; PCR	1	0	1	0	2	0	4	0
Soweto, South Africa (Aug 2011 – Aug 2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	NPS/OPS, Induced Sputum; PCR	46	4.3	33	9.1	32	0	111	4.5
Sa Kaeo, Thailand (Jan 2012–Dec 2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	NP/OP and induced sputum; PCR	..	..	3	0	3	0	6	0
Dhaka, Bangladesh (Jan 2012 – Dec 2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	NPS/OPS, Induced Sputum; PCR	6	0	10	0	13	0	29	0
Kilifi, Kenya (Aug 2011 – Nov 2011) (Deloria-Knoll and colleagues, unpublished)	ALRI	NPS/OPS, Induced Sputum; PCR	17	5.9	20	0	35	2.9	72	2.8

Location (reference)	Case definition	Specimen and test	0 –5 m		6–11 m		12–59 m		0–59 m	
			Cases (No.)	hCFR (%)	Cases (No.)	hCFR (%)	Cases (No.)	hCFR (%)	Cases (No.)	hCFR (%)
Bamako, Mali (Jan 2012 – Jan 2014) (Deloria-Knoll and colleagues, unpublished)	ALRI	NPS/OPS, Induced Sputum; PCR	39	5.1	32	18.8	29	10.3	100	11
Rabat, Morocco (Nov 2010–Dec 2011) (Bassat and colleagues, unpublished)	ALRI	NPA; PCR	21	9.5	20	0	116	3.4	157	3.8
Buenos Aires, Argentina (2000–2017) (Gentile and colleagues, unpublished)	ALRI	NPA; IFA	140	2.1	134	5.2	110	3.6	384	3.6
Manhiça, Mozambique (Jan 2011–Jul 2014) (Bassat and colleagues, unpublished)	ALRI	NPA; PCR	16	0	11	0	18	0	45	0
Iquique, Chile (2012–2013) (Fasce and colleagues, unpublished)	ALRI	NPA; IF	5	0	2	0	7	0	14	0
Concepcion, Chile (2012–2013) (Fasce and colleagues, unpublished)	ALRI	NPA; IF	10	0	6	0	16	0	32	0
Soweto, South Africa (Mar 1998–Oct 2005) (Madhi and colleagues, unpublished)	ALRI	NPA; IFA	35	5.7	32	3.1	21	0	88	3.4
Paarl, South Africa (Jun 2012–Dec 2017) (Zar and colleagues, unpublished)	ALRI	NPS; PCR	13	7.7	9	0	9	0	31	3.2
Klerksdorp, South Africa (2010–2015) (Cohen and colleagues, unpublished)	ALRI	NPA; PCR	37	0	31	3.2	49	2	117	1.7
Pietermaritzburg, South Africa (2010–2015) (Cohen and colleagues, unpublished)	ALRI	NPA; PCR	59	1.7	42	0	60	1.7	161	1.2
Colorado, United States of America (2010–2016) (Simões and colleagues, unpublished)	ALRI	NW; PCR (and DFA)	129	0.8	105	1.9	484	1.2	718	1.3
Berlin, Germany (Jan 2010–Dec 2014) (Rath and colleagues, unpublished)	ALRI	NPS; PCR	52	1.9	38	0	104	0	194	0.5
Taclobal City, Philippines (May 2008–Feb 2015) (Oshitani and colleagues, unpublished)	ALRI	NPS; PCR	28	14.3	24	4.2	27	3.7	79	7.6

Table A19–3e. hPIV – Description of included studies reporting proportions of hospitalised hPIV–associated ALRI cases in children younger than five years*†

Location (reference)	Case definition	Specimen and test	0–5 m		6–11 m		12–59 m		0–59 m	
			Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)
São Paulo city, Brazil (2008–2010) (Durigon et al. 2015)	ARI	NPA; PCR	..	..	..	..	..	..	..	..
Paris, France (2002–2004) (El-Hajje et al. 2008)	ALRI	NPA; IF	41	14.6	..	..	..	..	..	..
Hamburg, Dresden, Freiburg, Bochum, Germany (1999–2001) (Forster et al. 2004)	ALRI; croup	NP secretion; PCR	..	..	..	..	..	..	..	..
Montpellier, France (2003–2004) (Foulongne et al. 2006)	ARI	NPA; DFA and viral culture	..	..	..	..	..	..	602	1.5
Buenos Aires, Argentina (CEMIC) (1998–2002) (Galiano et al. 2004)	ALRI	NPA and NPS; IFA	..	..	..	..	..	..	440	2.3
Aracaju´, Salvador, Recife, and Maceio, Brazil (2012–2013) (Gurgel et al. 2016)	ALRI	NPA; PCR	..	..	..	..	..	..	..	..
Sa Kaeo and Nakhon Phanom, Thailand (2005–2010) (Hasan et al. 2014)	ARI	NPS and serum specimens; PCR, serologic test and culture	397	6.3	..	..	..	..	3810	9.1

* ARI: hospitalised acute respiratory infections. ALRI: physician diagnosed acute lower respiratory infections requiring hospital admission. ARI–Fever: hospitalised acute respiratory infections with fever. All: all diagnosis related to influenza (including influenza & pneumonia and other non-respiratory illnesses). NS: nasal swab. TS: throat swab. NW: nasal wash. PCR: polymerase chain reaction. NPA: nasopharyngeal aspirate. NPS: nasopharyngeal swab. OPS: oropharyngeal swab. NPW: nasopharyngeal wash. IFA: indirect immunofluorescence assay. DFA: direct immunofluorescence assay. IF: immunofluorescence. EIA: enzyme immunoassay. ELISA: enzyme-linked immunosorbent assay. BAL: bronchoalveolar lavage. APAAP: alkaline phosphatase and monoclonal anti–alkaline phosphatase.

† ..: not available. Some included studies did not provide data for 0 –5 m, 6–11 m , 12–59 m, or 0–59 m while provided data for other age groups (e.g., 0–23 m).

Location (reference)	Case definition	Specimen and test	0–5 m		6–11 m		12–59 m		0–59 m	
			Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)
Milwaukee County, USA (1996–1998) (Henrickson et al. 2004)	ALRI; croup	mainly NPS; EIA, culture, PCR	--	--	--	--	--	--	2750	12.5
Reims, France (2007–2008) (Huguenin et al. 2012)	ALRI	NPA; PCR	--	--	--	--	--	--	--	--
Yaounde, Cameroon (2011–2013) (Kenmoe et al. 2016)	ARI–Fever	NPS; PCR	--	--	--	--	--	--	307	6.8
Seeb, Oman (2007–2008) (Khamis et al. 2012)	ARI	NPA; PCR	--	--	--	--	--	--	518	7.7
Kuala Lumpur, Malaysia (1992–2008) (Khor et al. 2012)	ARI	mixed specimen; DFA and culture	3319	2.9	4241	4	2709	3.4	10269	3.5
Kumasi, Ghana (2008) (Kwofie et al. 2012)	ALRI	NPS; PCR	30	0	--	--	--	--	128	3.9
Shandong, China (2011–2013) (Liu et al. 2015)	ARI–Fever	TS; PCR	--	--	--	--	--	--	243	9.5
Shanghai, China (2013–2015) (Lu et al. 2017)	ALRI	NPA; DFA	--	--	--	--	--	--	--	--
Sioux Lookout, Ontario, Canada (2007–2012) (McCuskee et al. 2014)	ALRI	NA; immunochromatography assay and culture	--	--	--	--	--	--	--	--
São Paulo city, Brazil (2005–2007) (Pecchini et al. 2015)	ARI–Fever; ARI	NP secretion; IFA	--	--	--	--	--	--	510	8
Chonburi, Thailand (2013–2014) (Pratheepamornkull et al. 2015)	ALRI	NP specimen; PCR	--	--	--	--	--	--	102	2
Yukon Kuskokwim Delta, USA (2005–2007) (Singleton et al. 2010)	ALRI	NP specimens; PCR	--	--	--	--	--	--	--	--
Porto Alegre, Brazil (1992) (Straliotto et al. 2002)	ARI–Fever; ARI	NP secretion; IFA	--	--	--	--	--	--	42	2.4

Location (reference)	Case definition	Specimen and test	0–5 m		6–11 m		12–59 m		0–59 m	
			Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)
Zhejiang, China (2001–2006) (Tang et al. 2008)	ALRI	NPA; IFA	--	--	--	--	--	--	--	--
Taiwan (1997–1999) (Tsai et al. 2001)	ARI	TS and NPA; Culture	524	0	522	0.8	--	--	--	--
Buenos Aires city and Greater Buenos Aires, Argentina (1998–2002) (Viegas et al. 2004)	ALRI	NPA; IFA	--	--	--	--	--	--	18561	1.6
Beijing, China (2004–2012) (Wang et al. 2015)	Fever; ARI	NPA; DFA	8538	6.2	4077	10.3	--	--	21815	7.4
Shenzhen, China (2012–2015) (Wang et al. 2016)	ARI–Fever	NPS; DFA	--	--	--	--	--	--	--	--
Arizona, USA (2010–2014) (Wansaula et al. 2016)	ARI–Fever; ALRI	NPS; PCR	--	--	--	--	--	--	17	17.6
NVSN sites, USA (2000–2004) (Weinberg et al. 2009)	Fever; ARI	NS and TS; PCR	1324	4.4	386	8.8	--	--	2798	6.8
Beersheba, Israel (2001–2005) (Wolf et al. 2010)	ALRI	NPW; DFA and culture	--	--	--	--	--	--	997	3.1
Changsha, China (2010–2011) (Xiao et al. 2016)	ALRI	NPA; PCR	--	--	--	--	--	--	707	21.4
Milan, Italy (2004–2008) (Zappa et al. 2011)	ALRI	Pharyngeal swabs; PCR	144	0	36	0	--	--	--	--
Mirzapur, Bangladesh (1993–1994) ('The importance of viral infection in pneumonia among children under age 2 years' 2006)	ALRI	NPA; ELISA	--	--	--	--	--	--	--	--
ACH, Abha, Saudi Arabia (1997–2001) (Al-Shehri et al. 2005)	ALRI	NPA; ELISA and IFA	--	--	--	--	18	33.3	51	17.6

Location (reference)	Case definition	Specimen and test	0–5 m		6–11 m		12–59 m		0–59 m	
			Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)
KKUH, Riyadh, Saudi Arabia (1993–1996) (Bakir et al. 1998)	ALRI–Fever; ALRI	NPA; IFA and culture	--	--	--	--	--	--	1429	3.6
Riyadh, Saudi Arabia (2005–2010) (Bukhari and Elhazmi 2013)	ALRI	NPA; DFA	342	1.5	131	0	--	--	--	--
Hainan, China (2014) (Chen 2016)	ALRI	NPA; PCR	--	--	--	--	--	--	--	--
Ho Chi Minh City, Vietnam (2009–2010) (Do et al. 2016)	ARI	NPS; PCR	--	--	--	--	--	--	--	--
Seoul, Korea (2011–2012) (Eem et al. 2014)	ARI	NPS; PCR	--	--	--	--	--	--	--	--
Tokyo, Japan (2007–2012) (Hamada et al. 2014)	ALRI	NS; PCR	--	--	--	--	--	--	--	--
Lanzhou, China (2011) (Huang et al. 2013)	ARI	TS; PCR	--	--	--	--	--	--	--	--
Haryana, India (2009–2011) (Broor et al. 2014b)	All	NS and TS; PCR	--	--	--	--	--	--	245	4.1
Shijiazhuang, China (2014–2015) (Li et al. 2016)	ALRI	TS; DFA	1677	8.5	1274	11.9	--	--	--	--
Guangzhou, China (2009–2014) (Liao et al. 2015)	ARI	Pharyngeal swabs; PCR	--	--	--	--	--	--	--	--
Beijing, China (2010–2012) (Liu et al. 2013)	ARI	TS; PCR	--	--	--	--	--	--	--	--
Perth, Australia (2000–2005) (Moore et al. 2012)	ALRI	NPA; DFA, PCR and culture	--	--	--	--	--	--	5520	5.4
San Luis Potosi´, Mexico (2002–2004) (Noyola et al. 2005)	ARI	NW; PCR	--	--	--	--	--	--	--	--
Leganes, Madrid, Spain (2005–2008) (Calvo et al. 2010)	ALRI	NPA; PCR	--	--	--	--	--	--	--	--
Shantou, China (2007) (Ou et al. 2009)	ALRI	NPA; PCR	--	--	--	--	--	--	345	10.7

Location (reference)	Case definition	Specimen and test	0–5 m		6–11 m		12–59 m		0–59 m	
			Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)
Warsaw, Poland (2008–2011) (Pancer et al. 2014)	ARI	NPS; PCR and EIA	--	--	--	--	--	--	297	6.1
Chongqing, China (2014) (Peng et al. 2015)	ALRI	NPA; PCR	--	--	--	--	--	--	--	--
Cordoba, Spain (2011) (Rodriguez et al. 2016)	ARI	NPA; DFA	--	--	--	--	--	--	223	5.8
King George's Medical University, Lucknow, India (2011–2012) (Singh et al. 2014)	ALRI	NPA; PCR	--	--	--	--	85	0	155	0
Amphoe Takhli, Thailand (1998–2001) (Siritantikorn et al. 2002)	ALRI; croup	NPA; IFA	--	--	--	--	--	--	421	5.5
Rio de Janeiro, Brazil (1987–1989) (Sutmoller et al. 1995)	ALRI	NPA; IFA	--	--	--	--	--	--	241	0.8
Paraguay (2009) (Vázquez et al. 2011)	ALRI	NS, pharyngeal samples, NPA and BAL; PCR	--	--	--	--	--	--	367	6
Suzhou, Jiangsu, China (2007–2008) (Wan et al. 2009)	ARI	NPA; PCR	563	3.9	507	4.3	--	--	--	--
Hangzhou, China (2001–2003) (Wang et al. 2005)	ALRI	NPA; DFA	--	--	--	--	--	--	--	--
Kiel, Germany (1996–2000) (Weigl et al. 2005)	ALRI; croup	NPA; PCR	--	--	--	--	217	4.6	443	2.9
Changsha, China (2007–2008) (Xiao et al. 2012)	ALRI	NPA; PCR	350	14.3	320	17.5	453	13.9	1123	15
Beijing, China (2011–2012) (Zhang et al. 2015)	ALRI	Tracheal aspirate; PCR	--	--	--	--	--	--	--	--
Dhaka, Bangladesh (2014–2015) (Bhuyan et al. 2017)	ARI	NS; PCR	--	--	--	--	43	4.7	200	11
Seoul, Korea (1996–1998) (Ahn et al. 1999)	ALRI; croup	NPA; IFA	37	29.7	62	29	--	--	--	--
Spain (2011–2013) (Cebey-López et al. 2015)	ALRI	NP specimens; PCR	--	--	--	--	--	--	--	--

Location (reference)	Case definition	Specimen and test	0–5 m		6–11 m		12–59 m		0–59 m	
			Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)
London, UK (2009–2012) (Cebey-López et al. 2015)	ALRI	NP specimens; PCR	--	--	--	--	--	--	--	--
Nicosia, Cyprus (2010–2013) (Richter et al. 2016)	ARI	NS; PCR	--	--	--	--	--	--	--	--
Egypt (2007–2014) (Horton et al. 2017b)	ARI	NPS and OPS; PCR	--	--	--	--	1486	10.1	3292	10.1
Jordan (2008–2010) (Horton et al. 2017b)	ARI	NPS and OPS; PCR	--	--	--	--	249	9.6	578	9.2
Oman (2008–2009) (Horton et al. 2017b)	ARI	NPS and OPS; PCR	--	--	--	--	220	10.5	473	8.5
Qatar (2008–2009) (Horton et al. 2017b)	ARI	NPS and OPS; PCR	--	--	--	--	6	0	15	6.7
Yemen (2010–2014) (Horton et al. 2017b)	ARI	NPS and OPS; PCR	--	--	--	--	169	11.8	628	10
Manhica, Mozambique (2006–2007) (O'Callaghan-Gordo et al. 2011)	ALRI	NPA; PCR	--	--	--	--	--	--	807	3.8
Asembo, Kenya (2007–2010) (Feikin et al. 2013)	ALRI	NPS or OPS; PCR	--	--	--	--	--	--	350	10
Shenzhen, China (2007–2010) (He et al. 2014)	ARI	NPA; PCR	595	7.9	408	9.1	812	9.1	1815	8.7
Recife, Brazil (2008–2009) (Bezerra et al. 2011)	ARI	NPA; PCR	--	--	--	--	--	--	211	8.5
Navajo and White Mountain Apache, USA (2009) (Bhat et al. 2013)	ALRI	NW; PCR	--	--	--	--	--	--	--	--
Cape Town, South Africa (2003–2004) (Smuts 2008)	ARI	NPA, tracheal aspirate, BAL; IFA	--	--	--	--	--	--	1055	4
Guangdong, China (2010–2011) (Xu et al. 2012)	ARI	TS; PCR	--	--	--	--	--	--	--	--
Gipuzkoa, Spain (2004–2007) (Cilla et al. 2009)	ARI; ARI–Fever	NPA; PCR and culture	386	6	153	11.8	--	--	--	--
Changsha, China (2012–2013) (彭颖 2014)	ALRI	NPA; PCR	143	48.3	159	42.1	293	34.1	595	39.7

Location (reference)	Case definition	Specimen and test	0–5 m		6–11 m		12–59 m		0–59 m	
			Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)
Shanghai, China (2003–2006) (曾玫 et al. 2008)	ARI	NPA; DFA	--	--	--	--	--	--	10240	3.8
Jiangxi, China (2011–2012) (付晶晶 et al. 2013)	ALRI	NPA; DFA	--	--	--	--	--	--	--	--
Wuhan, China (2012–2013) (杜帅先 et al. 2016)	ARI	NP secretions; DFA	--	--	--	--	--	--	--	--
Yanting, China (2011–2012) (何杨 2015)	ARI	NPA; PCR	--	--	--	--	--	--	--	--
Wuhan, China (2014) (杨泉 and 席金瓯 2016)	ARI	NPA; DFA	1342	3.3	1621	4.8	--	--	--	--
Qingyuan, China (2014–2015) (梁大立 et al. 2015)	ARI	NPS; DFA	--	--	--	--	--	--	--	--
Shaoxing, China (2011–2013) (章建伟 et al. 2014)	ARI	NPA; DFA	1854	6.9	672	5.2	--	--	--	--
Nanjing, China (2013–2014) (胡剑 et al. 2015)	ALRI	NP secretions; DFA	240	5.8	94	9.6	--	--	--	--
Zhuzhou, China (2011) (蒋最明 et al. 2013)	ARI	NPA; DFA	--	--	--	--	--	--	--	--
Nanjing, China (2009–2012) (赵艳丰 et al. 2013)	ARI	NP secretions; DFA	--	--	--	--	--	--	--	--
Shanghai, China (2000) (车大钿 et al. 2004)	ALRI	NPA; APAAP	--	--	--	--	--	--	1027	22.7
Mianyang, China (2014–2015) (邓益斌 et al. 2016)	ARI	NPS; IFA	--	--	--	--	--	--	--	--
Suzhou, China (2006–2015) (任吟莹 et al. 2017)	ARI	NPA; DFA	--	--	--	--	--	--	29389	2.7
Chenzhou, China (2013–2014) (吴琼 et al. 2017)	ARI–Fever	NS; PCR	--	--	--	--	--	--	489	17.6
Wenzhou, China (2014) (张海邻 et al. 2017)	ALRI	NPA; DFA	--	--	--	--	--	--	922	15.7
Wuxi, China (2014–2015) (杨俊钧 et al. 2017)	ARI	NPS; DFA	--	--	--	--	--	--	--	--

Location (reference)	Case definition	Specimen and test	0–5 m		6–11 m		12–59 m		0–59 m	
			Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)
Guangzhou, China (2015) (蔡勇 et al. 2017)	ARI	NPS; PCR	216	7.4	310	8.1	..	..	..	..
Changsha, China (2015) (谢红军 and 李征 2017)	ARI	NPS; DFA	..	..	..	..	..	..	..	..
Jiujiang, China (2016) (赵旦 et al. 2017)	ARI	NP secretion; DFA	2163	2.8	..	..	..	..	..	..
Yangzhou, China (2013–2015) (金玉 et al. 2017)	ARI	NP secretion; DFA	567	12.7	435	11	..	..	..	..
Bengbu, China (2015–2016) (阴睿媛 et al. 2017)	ARI	NP secretion; DFA	229	3.9	122	6.6	..	..	..	..
Guangzhou, China (2009–2010) (颉雅苹 and 邓力)	ALRI	NPS; PCR	..	..	..	..	..	..	..	..
Shanghai, China (2001–2002) (赵国昌 et al. 2003)	ALRI	nasotracheal aspiration; APAAP	233	3.4	134	0.7	..	..	..	..
Nanjing, China (2006–2007) (秦铭 et al.)	ALRI	NPA; DFA	199	1.5	207	4.8	449	9.4	855	6.4
Wenzhou, China (2003–2006) (曹淑彦 et al. 2007)	ARI	NP secretion; DFA	..	..	..	..	..	..	..	..
Baiyin, China (2012–2013) (于德山 et al. 2017)	ALRI	NPA; PCR	20	20	93	23.7	..	..	391	18.2
Guangxi, China (2013) (张海琼 and 俞小珍 2015)	ALRI	NPS; DFA	..	..	..	..	..	..	..	..
Lanzhou, China (2010–2011) (曹海燕 2013)	ARI	NPA; PCR	166	21.7	130	36.2	174	20.7	470	25.3
Shijiazhuang, China (2015–2016) (王胜娥 2016)	ALRI	BALF; PCR	..	..	..	..	274	15.3	351	17.4
Suzhou, China (2011–2016) (赵凯 et al. 2017)	ALRI	NPA; DFA	..	..	..	..	..	..	..	..
Xi'an, China (1994–1997) (张艳敏 et al.)	ALRI	NP secretion; APAAP	65	20	52	15.4	..	..	..	..
Dujiangyan, China (2007–2009) (曹淑彦 et al. 2007)	ALRI	NPA; IFA	..	..	..	..	..	..	..	..

Location (reference)	Case definition	Specimen and test	0–5 m		6–11 m		12–59 m		0–59 m	
			Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)
Fuzhou, China (1996–1997) (刘晖 and 陈敏 1999)	ALRI	NP secretion; APAAP	99	9.1	128	13.3	--	--	--	--
Kunming, China (2005–2007) (李杨方 et al. 2008)	ALRI	NPA; IFA	--	--	--	--	--	--	--	--
Hangzhou, China (2001–2003) (马晓路 et al. 2005)	ALRI	NPA; DFA	--	--	--	--	--	--	--	--
Changsha, China (2013–2014) (刘沁 et al. 2015)	ALRI	NPA; PCR	138	21	142	31	262	23.7	542	24.9
Chongqing, China (2009–2012) (卢庆彬 2013)	ARI	NPA; PCR	1028	24.7	506	26.7	739	21.4	2273	24.1
Chenzhou, China (2010) (史文元 et al. 2012)	ALRI	NP secretions; PCR	--	--	--	--	--	--	--	--
Kunming, China (2005–2006) (吴茜 et al. 2007)	ALRI	NPA; DFA	--	--	--	--	--	--	--	--
Jinhua, China (2013–2014) (吴远桥 2015)	ARI	NPS; DFA	411	13.4	324	6.5	--	--	--	--
Suzhou, China (2009–2013) (尹芳 2014)	ARI	NP secretions; DFA	5404	4.7	2942	6.2	--	--	13653	6.1
Zhejiang, China (2006–2010) (张冰 et al. 2012)	ALRI	NPA; DFA	--	--	--	--	--	--	3932	3.9
Foshan, China (2013–2014) (张巧玲 et al. 2014)	ALRI	NP specimens; DFA	424	8.5	506	12.3	--	--	1922	10.8
Chengdu, China (2007) (张蕾 2008)	ALRI	NP specimens; DFA	--	--	--	--	--	--	--	--
Shanghai, China (2011–2012) (张雪清 et al. 2013)	ALRI	NP secretions; DFA	--	--	--	--	--	--	--	--
Kawayan and Caibiran, Philippines (2014–2016) (Oshitani and colleagues, unpublished	ALRI	NPS; PCR	39	7.7	28	17.9	56	7.1	123	9.8
Naval, Philippines (Sep 2012–Jul 2016) (Oshitani	ALRI	NPS; PCR	451	4.4	218	8.7	423	6.6	1092	6.1

Location (reference)	Case definition	Specimen and test	0–5 m		6–11 m		12–59 m		0–59 m	
			Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)
and colleagues, unpublished)										
Muntinlupa, Philippines (Sep 2012–Feb 2015) (Oshitani and colleagues, unpublished)	ALRI	NPS; PCR	70	1.4	59	1.7	59	1.7	188	1.6
Ospital ng Palawan, Philippines (Aug 2012–Feb 2015) (Oshitani and colleagues, unpublished)	ALRI	NPS; PCR	236	3	166	3	292	5.5	694	4
Kilifi, Kenya (2007–2017) (Nokes and colleagues, unpublished)	ALRI	NPS; PCR	1347	7.9	759	8.3	1265	7.3	3371	7.7
Nha Trang city, Viet Nam (2007–2016) (Yoshida and colleagues, unpublished)	ALRI	NPS; PCR	261	7.3	205	8.3	979	7.4	1445	7.5
Buenos Aires, Argentina (Jun 2008–Dec 2010) (Echavarria and colleagues, unpublished)	ARI	NPA; IFA	12	8.3	18	5.6	43	11.6	73	9.6
multiple areas, Philippines (Jul 2000–Dec 2004) (Lucero and colleagues, unpublished)	ALRI	Blood, NPS and NPA; Serum and culture	233	15	278	12.6	..	..	..	..
Amman, Jordan (Mar 2010–Mar 2013) (Khuri-Bulos and colleagues, unpublished)	ALRI	Nasal and throat swabs; PCR	..	..	..	..	..	..	..	..
multiple areas, Bangladesh (2010–2014) (Homaira and colleagues, unpublished)	ARI–Fever; ALRI	Nasal and throat swabs; PCR	451	6	198	8.1	182	8.2	831	7
Matlab, Bangladesh (Jan 2012 – Dec 2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	NPS/OPS, Induced Sputum; PCR	94	9.6	74	10.8	159	15.7	327	12.8

Location (reference)	Case definition	Specimen and test	0–5 m		6–11 m		12–59 m		0–59 m	
			Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)
Basse, Gambia (2012–2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	NPS/OPS, Induced Sputum; PCR	256	19.5	138	31.2	229	17	623	21.2
Lusaka, Zambia (Oct 2011 – Oct 2014) (Deloria-Knoll and colleagues, unpublished)	ALRI	NPS/OPS, Induced Sputum; PCR	314	8.3	143	16.8	133	12.8	590	11.4
Nakhon Phanom, Thailand (Jan 2012–Dec 2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	NP/OP and induced sputum; PCR	9	11.1	13	7.7	51	3.9	73	5.5
Soweto, South Africa (Aug 2011 – Aug 2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	NPS/OPS, Induced Sputum; PCR	431	10.7	212	15.6	223	14.3	866	12.8
Sa Kaeo, Thailand (Jan 2012–Dec 2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	NP/OP and induced sputum; PCR	7	0	11	27.3	33	9.1	51	11.8
Dhaka, Bangladesh (Jan 2012 – Dec 2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	NPS/OPS, Induced Sputum; PCR	42	14.3	47	21.3	109	11.9	198	14.6
Kilifi, Kenya (Aug 2011 – Nov 2011) (Deloria-Knoll and colleagues, unpublished)	ALRI	NPS/OPS, Induced Sputum; PCR	185	9.2	116	17.2	265	13.2	566	12.7
Bamako, Mali (Jan 2012 – Jan 2014) (Deloria-Knoll and colleagues, unpublished)	ALRI	NPS/OPS, Induced Sputum; PCR	297	13.1	151	21.2	211	13.7	659	15.2
Rabat, Morocco (Nov 2010–Dec 2011) (Bassat and colleagues, unpublished)	ALRI	NPA; PCR	100	19	112	16.1	419	24.6	631	22.2

Location (reference)	Case definition	Specimen and test	0–5 m		6–11 m		12–59 m		0–59 m	
			Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)
Buenos Aires, Argentina (2000–2017) (Gentile and colleagues, unpublished)	ALRI	NPA; IFA	4674	3	3634	3.7	4016	2.7	12311	3.1
Manhiça, Mozambique (Jan 2011–Jul 2014) (Bassat and colleagues, unpublished)	ALRI	NPA; PCR	114	14	96	11.5	203	6.9	413	9.9
Iquique, Chile (2012–2013) (Fasce and colleagues, unpublished)	ALRI	NPA; IF	312	3.2	148	5.4	217	6	677	4.6
Concepcion, Chile (2012–2013) (Fasce and colleagues, unpublished)	ALRI	NPA; IF	216	4.6	85	7.1	163	9.8	464	6.9
Tehran, Iran (Islamic Republic of) (2008–2009) (Vahid and colleagues, unpublished)	ARI–Fever	Throat swabs and washes; PCR	..	..	..	..	..	..	80	18.8
Tehran, Iran (Islamic Republic of) (2017) (Vahid and colleagues, unpublished)	ARI–Fever	NP secretions; IFA	..	..	..	..	..	..	100	26
Tehran, Iran (Islamic Republic of) (Sep 2012–Sep 2013) (Vahid and colleagues, unpublished)	ARI–Fever	Throat swabs; PCR	..	..	..	..	..	..	78	15.4
Tehran, Iran (Islamic Republic of) (Jan 2003 to Jan 2004) (Vahid and colleagues, unpublished)	ARI–Fever	NP secretions; IFA	11	18.2	30	43.3	55	18.2	96	26
Tehran, Iran (Islamic Republic of) (Oct 1998–Oct 2000) (Vahid and colleagues, unpublished)	ARI	NPS; Culture	..	..	..	..	111	18	200	17.5
Soweto, South Africa (Mar 1998–Oct 2005) (Madhi and colleagues, unpublished)	ALRI	NPA; IFA	962	3.6	605	5.3	1035	2	2602	3.4

Location (reference)	Case definition	Specimen and test	0–5 m		6–11 m		12–59 m		0–59 m	
			Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)	Tested ALRI (No.)	Proportion of hPIV (%)
Kamalapur, Bangladesh (2013–2014) (Brooks and colleagues, unpublished)	ALRI	NPW; PCR	19	5.3	16	12.5	32	0	67	4.5
Paarl, South Africa (Jun 2012–Dec 2017) (Zar and colleagues, unpublished)	ALRI	NPS; PCR	102	12.7	42	21.4	57	15.8	201	15.4
Kathmandu and surrouning disctricts, Nepal (Jan 2006–Jan 2008) (Strand and colleagues, unpublished)	ALRI	NPA; PCR	248	8.1	173	6.9	..	..	..	..
Klerksdorp, South Africa (2010–2015) (Cohen and colleagues, unpublished)	ALRI	NPA; PCR	504	7.3	269	11.5	486	10.1	1259	9.3
Pietermaritzburg, South Africa (2010–2015) (Cohen and colleagues, unpublished)	ALRI	NPA; PCR	883	6.7	442	9.5	746	8	2164	7.4
Berlin, Germany (Jan 2010–Dec 2014) (Rath and colleagues, unpublished)	ALRI	NPS; PCR	730	7.1	424	9	1358	7.7	2512	7.7
Taclobal City, Philippines (May 2008–Feb 2015) (Oshitani and colleagues, unpublished)	ALRI	NPS; PCR	816	2.9	510	3.9	1094	2.3	2420	2.9

Table A19–3f. hPIV – Description of included studies reporting hospitalisation rates of hPIV–associated ALRI with hypoxaemia (per 1,000 children per year)*†

Location (reference)	Case Definition	Denominator type	Specimen and test	0–5 m	6–11 m	11–23 m	24–59 m	0–59 m
Kawayan and Caibiran, Philippines (2014–2016) (Oshitani and colleagues, unpublished	ALRI	Defined population base	NPS; PCR	0	0	0	0	0
Kilifi, Kenya (2007–2017) (Nokes and colleagues, unpublished)	ALRI	Census derived estimate	NPS; PCR	2.5	1.2	0.7	0.1	0.6
Nha Trang city, Viet Nam (2007–2016) (Yoshida and colleagues, unpublished)	ALRI	Census derived estimate	NPS; PCR	..	..	0.2	0	0.1
Buenos Aires, Argentina (Jun 2008–Dec 2010) (Echavarria and colleagues, unpublished)	ARI	Defined population base	NPA; IFA	3	0	..	..	0.9
Amman, Jordan (Mar 2010–Mar 2013) (Khuri-Bulos and colleagues, unpublished)	ALRI	Census derived estimate	NS and TS; PCR	0.1	0.1	0	..	..
Basse, Gambia (2012–2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	Census derived estimate	NPS/OPS, Induced Sputum; PCR	0.9	0.3	0.1	0.1	0.2
Nakhon Phanom, Thailand (Jan 2012–Dec 2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	Census derived estimate	NP/OP and induced sputum; PCR	..	..	0	0	0.1
Sa Kaeo, Thailand (Jan 2012–Dec 2013) (Deloria-Knoll and colleagues, unpublished)	ALRI	Census derived estimate	NP/OP and induced sputum; PCR	..	..	0	0	0.1
Buenos Aires, Argentina (2000–2017) (Gentile and colleagues, unpublished)	ALRI	Defined population base	NPA; IFA	..	..	3.2	1	4
Manhiça, Mozambique (Jan 2011–Jul 2014) (Bassat and colleagues, unpublished)	ALRI	Defined population base	NPA; PCR	0.7	0.8	0.1	0.1	0.2
Soweto, South Africa (Mar 1998–Oct 2005) (Madhi and colleagues, unpublished)	ALRI	Defined population base	NPA; IFA	1.3	1	0.2	0	0.3
Kamalapur, Bangladesh (2013–2014) (Brooks and colleagues, unpublished)	ALRI	Defined population base	NPW; PCR	0.8	0	0	0	0.3
Paarl, South Africa (Jun 2012–Dec 2017) (Zar and colleagues, unpublished)	ALRI	Defined population base	NPS; PCR	6	0	0	0	0.8

* ARI: hospitalised acute respiratory infections. ALRI: physician diagnosed acute lower respiratory infections requiring hospital admission. NS: nasal swab. TS: throat swab. PCR: polymerase chain reaction. NPA: nasopharyngeal aspirate. NPS: nasopharyngeal swab. OPS: oropharyngeal swab. NPW: nasopharyngeal wash. IFA: indirect immunofluorescence assay.
† ..: not available.

A20. Details of risk of bias in individual studies

Table A19–1a. IFV – Quality studies reporting incidence rates of IFV–diseases in children under five years by severity*†

Disease‡	Location (Period of study)	Study design	Patient group excluded	Case definition	Sampling strategy	Diagnostic test
Episode	Vietnam;2007–2010	Low	Low	Low	Low	Low
Episode	Mali;2011–2014	Low	Low	High	Low	Low
Episode	United States of America;2009–2013	Low	Low	High	Low	Low
Episode	Japan;2009–2011	High	Low	High	Low	Low
Episode	Finland;2000–2002	Low	High	Low	Low	Low
Episode	Senegal;2012–2013	Low	Low	High	Low	Low
Episode	Senegal;2012–2013	Low	Low	High	Low	Low
Episode	Japan;2002–2008	Low	High	High	Low	High
Episode	United States of America;1974–1999	Low	Low	High	Low	Low
Episode	Switzerland;1999–2004	Low	Low	Low	Low	Low
Episode	India;2001–2005	Low	Low	High	Low	High
Episode	Bangladesh;2004–2007	Low	Low	High	Low	Low
Episode	United States of America;2010–2014	High	High	High	High	High
Episode	India;2012–2014	Low	High	High	High	Low
Episode	Australia;2011	Low	High	Low	Low	Low
Episode	Nepal;2011–2013	Low	Low	High	Low	Low
Episode	Southwest Finland;2010–2012	Low	Low	High	Low	Low
Episode	Japan;2004–2008	Low	Low	Low	High	High
Episode	Nicaragua;2012–2015	Low	Low	High	Low	Low
Episode	Bangladesh;2007–2015	Low	Low	Low	Low	Low
Episode	Nepal;2011–2014	Low	Low	High	Low	Low
Episode	Mali;2011–2014	Low	Low	High	Low	Low
Episode	South Africa;2011–2013	Low	Low	High	Low	Low
Episode	Australia; 2010–2014	Low	High	High	High	Low
Episode	Romania; 2011–2016	High	Low	Low	Low	Low
Episode	Nepal; 2011–2013	Low	Low	High	High	Low
Episode	Spain; 2011–2016	Low	Low	High	High	Low
ALRI	Finland;2000–2002	Low	High	Low	Low	Low
ALRI	Germany;1999–2001	Low	Low	High	High	Low
ALRI	United States of America;1974–1999	Low	Low	Low	Low	Low
ALRI	India;2001–2005	Low	Low	Low	Low	High
ALRI	Bangladesh;2004–2007	Low	Low	Low	Low	Low

* Only in community-based studies
† Low: low risk of bias; high: high risk of bias
‡ Episode: for IFV-episode. sALRI: chest wall indrawing ALRI. vsALRI: for very severe ALRI.

Disease‡	Location (Period of study)	Study design	Patient group excluded	Case definition	Sampling strategy	Diagnostic test
ALRI	India;2012–2014	Low	High	Low	High	Low
ALRI	India;2012–2014	Low	Low	Low	Low	Low
ALRI	Nicaragua;2012–2015	Low	Low	Low	Low	Low
ALRI	Bangladesh;2007–2015	Low	Low	Low	Low	Low
ALRI	Pakistan;2012–2014	Low	Low	Low	Low	Low
ALRI	South Africa;2012–2016	Low	Low	Low	Low	Low
ALRI	Australia; 2010–2014	Low	High	Low	High	Low
sALRI	Bangladesh;1993–1996	Low	Low	Low	Low	High
sALRI	Bangladesh;2004–2007	Low	Low	Low	Low	Low
sALRI	India;2012–2014	Low	Low	Low	Low	Low
sALRI	Nicaragua;2012–2015	Low	Low	Low	Low	Low
sALRI	Bangladesh;2007–2015	Low	Low	Low	Low	Low
sALRI	Pakistan;2011–2014	Low	Low	Low	Low	Low
sALRI	South Africa;2012–2016	Low	Low	Low	Low	Low
sALRI	Bangladesh;2011–2013	Low	Low	High	Low	Low
sALRI	Pakistan;2012–2013	Low	Low	High	Low	Low
sALRI	Pakistan;2012–2013	Low	Low	High	Low	Low
sALRI	India;2013–2014	Low	Low	High	Low	Low
sALRI	India;2013–2014	Low	Low	High	Low	Low
sALRI	Nepal;2011–2014	Low	Low	Low	Low	Low
sALRI	Mali;2011–2014	Low	Low	Low	Low	Low
vsALRI	India;2012–2014	Low	Low	Low	Low	Low
vsALRI	Nicaragua;2012–2015	Low	Low	Low	Low	Low
vsALRI	Bangladesh;2007–2015	Low	Low	Low	Low	Low
vsALRI	South Africa;2012–2016	Low	Low	Low	Low	Low

Table A19–1b. IFV – Quality of studies reporting hospitalisation rates of IFV–(severe and very severe) ALRI in children under five years*

Location (Period)	Study design	Adjustment for health utilization †	Patient group excluded	Case definition	Sampling strategy	Diagnostic test	Hypoxaemia‡
United States of America;2003–2012	Low	Low	Low	High	High	High	NA
Hong Kong;2004–2011§	Low	Low	Low	High	Low	Low	NA
Australia;1997–2013	High	Low	Low	Low	High	High	NA
Hong Kong;2005–2011	High	Low	Low	High	High	Low	NA
United States of America;2003–2010	Low	Low	Low	High	High	High	NA
Bangladesh;2010–2014	Low	Low	Low	High	Low	Low	NA
Denmark;2009–2011	High	Low	Low	Low	High	Low	NA
Philippines;2009–2011	Low	High	Low	High	Low	Low	NA
France;2009–2013	High	Low	Low	Low	High	High	NA
China;2010–2012	Low	Low	Low	High	Low	Low	NA
Taiwan;2009–2011	High	Low	Low	Low	High	Low	NA
El Salvador;2009–2012	High	Low	Low	High	Low	High	NA
Guatemala;2009–2012	High	Low	Low	High	Low	High	NA
Honduras;2009–2012	High	Low	Low	High	Low	High	NA
Nicaragua;2009–2012	High	Low	Low	High	Low	High	NA
Oman;2008–2013	Low	Low	Low	Low	Low	Low	NA
Oman;2008–2013	Low	Low	Low	High	Low	Low	NA
Oman;2008–2013	Low	Low	Low	High	Low	Low	NA
Kenya;2007–2009	Low	Low	Low	Low	Low	Low	NA
Germany;1999–2001	Low	Low	Low	High	Low	Low	NA
United States of America;2003–2008	Low	Low	Low	High	High	High	NA
Germany;1996–2000	High	Low	Low	High	Low	Low	NA
Spain;2001–2004	High	Low	Low	High	Low	Low	NA
United Kingdom;2002–2004	Low	Low	Low	High	Low	Low	NA
United Kingdom;2001–2002	Low	Low	Low	High	High	Low	NA

* Low: low risk of bias; high: high risk of bias
† Only for studies reporting hospitalisation rates
‡ NA: not applicable.
§ Combining Flu A and B in study ID - e12.

Location (Period)	Study design	Adjustment for health utilization †	Patient group excluded	Case definition	Sampling strategy	Diagnostic test	Hypoxaemia‡
Spain;1997–2003	High	Low	Low	High	High	Low	NA
Vietnam;2007–2008	Low	Low	Low	High	Low	Low	NA
Hong Kong;1997–1999	High	Low	Low	High	High	Low	NA
Hong Kong;2003–2006	Low	Low	Low	High	Low	High	NA
China;2007–2008	High	High	Low	High	High	High	NA
Australia;1996–2006	High	Low	Low	High	High	Low	NA
United States of America;2001–2004	Low	Low	Low	High	Low	Low	NA
United States of America;2000–2001	Low	Low	Low	High	Low	Low	NA
United States of America;2001–2004	High	Low	Low	High	High	High	NA
United States of America;2000–2004	High	High	Low	High	High	Low	NA
United States of America;2003–2005	Low	Low	Low	High	Low	High	NA
Japan;2002–2008	Low	Low	Low	High	Low	High	NA
United States of America;1996–1998	High	Low	Low	High	High	High	NA
Brazil;1987–1989	Low	High	Low	Low	Low	Low	NA
United States of America;1974–1999	Low	Low	Low	High	Low	Low	NA
Guatemala;2008	Low	Low	Low	High	Low	Low	NA
Mozambique;2006–2007	Low	Low	Low	Low	Low	Low	NA
Hong Kong;2004–2014	Low	Low	Low	High	Low	High	NA
Philippines;2012–2014	Low	Low	Low	High	Low	Low	NA
Ghana;2013–2015	Low	Low	High	High	Low	Low	NA
United Kingdom;2010–2015	Low	Low	Low	High	Low	Low	NA
Germany;2005–2012	High	Low	Low	High	High	High	NA
Australia;2006–2015	High	Low	Low	High	High	High	NA
United States of America;2010–2012	Low	Low	High	Low	Low	Low	NA
United States of America;2004–2009	Low	Low	Low	High	Low	Low	NA
Greece;2002–2005	Low	Low	Low	High	Low	Low	NA
Finland;1988–2004	Low	Low	Low	High	High	High	NA

Location (Period)	Study design	Adjustment for health utilization †	Patient group excluded	Case definition	Sampling strategy	Diagnostic test	Hypoxaemia‡
United Kingdom;2012–2013	High	Low	Low	Low	High	Low	NA
Spain;2011–2012	Low	Low	High	High	Low	Low	NA
United States of America;2010–2011	Low	Low	Low	High	High	High	NA
Multi–country; 2010–2014	Low	NA	High	Low	Low	Low	NA
Romania; 2016–2017	Low	NA	Low	High	Low	Low	NA
Multi–country; 2013	Low	NA	High	High	High	Low	NA
Georgia; 2014–2017	Low	NA	Low	High	Low	Low	NA
Mozambique; 2014–2016	Low	NA	Low	High	Low	Low	NA
Spain; 2010–2016	High	Low	Low	Low	High	Low	NA
Indonesia; 2013–2016	Low	Low	Low	High	Low	Low	NA
Spain; 2010–2015	Low	NA	Low	Low	Low	Low	NA
China; 2014–2015	High	NA	Low	Low	High	High	NA
China; 2016–2017	High	NA	Low	High	High	Low	NA
Congo, Dem. Rep; 2013–2015	Low	Low	Low	Low	Low	Low	NA
Cambodia; 2015–2016	Low	Low	Low	High	Low	Low	NA
Cambodia; 2015–2016	Low	Low	Low	High	Low	Low	NA
Cambodia; 2015–2016	Low	Low	Low	High	Low	Low	NA
Rwanda; 2012–2014	Low	Low	Low	High	Low	Low	NA
Chile; 2012–2014	Low	Low	Low	High	Low	Low	NA
China; 2014–2016	Low	Low	Low	High	High	Low	NA
China; 2017–2018	Low	Low	Low	High	Low	Low	NA
Oman; 2012–2015	High	Low	Low	High	High	Low	NA
Kenya;2010–2014	Low	Low	Low	Low	Low	Low	Low
Kenya;2010–2014	Low	Low	Low	Low	Low	Low	Low
Togo;2011–2013; 2014–2015	Low	Low	Low	Low	Low	Low	Low
South Africa;1998 to 2005	Low	Low	High	Low	Low	High	High
Jordan;2010–2013	Low	Low	Low	Low	Low	Low	Low
Mozambique;2011–2014	Low	High	Low	Low	Low	Low	Low
Kenya;2007–2016	Low	Low	Low	Low	Low	Low	Low
Thailand;2012–2013	Low	Low	High	Low	Low	Low	NA
Thailand;2012–2013	Low	Low	High	Low	Low	Low	NA
Vietnam;2008–2013	Low	Low	High	Low	Low	Low	Low

Location (Period)	Study design	Adjustment for health utilization †	Patient group excluded	Case definition	Sampling strategy	Diagnostic test	Hypoxaemia‡
Gambia;2011–2013	Low	Low	High	Low	Low	Low	NA
Israel;2011–2016	Low	High	Low	High	High	Low	NA
Thailand;2005–2011	Low	Low	Low	High	Low	Low	NA
India;2009–2013	Low	Low	Low	Low	Low	Low	High
Bangladesh;2007–2015	Low	Low	Low	Low	Low	Low	NA
Pakistan;2012–2014	Low	Low	Low	Low	High	Low	High
Argentina;2008–2010	Low	Low	High	Low	Low	High	High
Finland;2010–2012	Low	High	Low	Low	Low	High	NA
United States of America;2011–2015	High	High	Low	Low	High	High	High
South Africa;2012–2016	Low	Low	Low	Low	Low	Low	NA
Argentina;2011–2013	Low	Low	Low	Low	Low	Low	High
Guatemala;2010–2016	Low	Low	Low	Low	Low	Low	Low
Guatemala;2010–2016	Low	Low	Low	Low	Low	Low	Low
Philipines;2000–2004	Low	Low	High	Low	Low	Low	Low
Spain;2014–2017	Low	Low	Low	High	Low	Low	High
Argentina;2009–2016	Low	High	Low	Low	Low	Low	Low
South Africa;2015–2017	Low	Low	Low	Low	High	Low	NA
South Africa;2013–2015	Low	High	Low	Low	Low	Low	NA
South Africa;2013–2015	Low	High	Low	Low	Low	Low	NA
South Africa;2011–2013	Low	Low	Low	Low	Low	Low	NA
South Africa;2009–2012	Low	Low	Low	Low	Low	Low	NA
Chile;2012–2013	Low	High	Low	Low	Low	Low	NA
Chile;2012–2013	Low	High	Low	Low	Low	Low	NA

Table A19–1c. IFV – Quality of studies reporting IFV–ALRI in–hospital case fatality ratios (hCFRs) in children under five years*

Location (Period)	Study design	Patient group excluded	Case definition	Sampling strategy
Egypt, Jordan, Oman, Qatar and Yemen; 2007–2014	Low	Low	High	High
Argentina; 2009–2016	Low	Low	Low	Low
South Africa; 2013–2015	Low	Low	Low	Low
South Africa; 2013–2015	Low	Low	Low	Low
South Africa; 2009–2012	Low	Low	Low	Low
Chile; 2012–2013	Low	Low	Low	Low
Chile; 2012–2013	Low	Low	Low	Low
Kenya; 2010–2014	Low	Low	Low	High
Kenya; 2010–2014	Low	Low	Low	High
Togo; 2011–2013; 2014–2015	Low	Low	Low	Low
South Africa; 1998 to 2005	Low	High	Low	Low
Jordan; 2010–2013	Low	Low	Low	Low
Mozambique; 2011–2014	Low	Low	Low	Low
Kenya; 2007–2016	Low	Low	Low	High
Thailand; 2012–2013	Low	High	Low	Low
Thailand; 2012–2013	Low	High	Low	Low
Viet Nam; 2008–2013	Low	High	Low	Low
Germany; 2010–2014	Low	Low	Low	Low
Gambia; 2011–2013	Low	High	Low	Low
Thailand; 2005–2011	Low	Low	High	High
India; 2009–2013	Low	Low	Low	Low
Argentina; 2008–2010	Low	High	Low	Low
Finland; 2010–2012	Low	Low	Low	Low
United States of America; 2011–2015	High	Low	Low	High
Argentina; 2011–2013	Low	Low	Low	Low
Guatemala; 2010–2016	Low	Low	Low	Low
Guatemala; 2010–2016	Low	Low	Low	Low
Philippines; 2000–2004	Low	High	Low	High
Panama; 2012–2014	Low	Low	Low	High
Jordan, Oman, Egypt; 2007–2009	Low	Low	Low	Low
Guatemala; 2008	Low	Low	High	Low
Kenya; 2007–2009	Low	Low	Low	Low
Spain; 2001–2004	High	Low	High	Low
United Kingdom; 2001–2002	Low	Low	High	High
United States of America; 2001–2004	High	Low	High	High
United States of America; 2000–2004	High	Low	High	High
Australia; 1996–2006	High	Low	High	High
China; 2005	High	High	High	High

* Low: low risk of bias; high: high risk of bias.

Location (Period)	Study design	Patient group excluded	Case definition	Sampling strategy
Canada; 2003–2004	High	Low	High	High
United States of America; 2003–2008	Low	Low	High	High
Brazil; 1996–2001	High	Low	High	High
China; 1997–1999	High	Low	High	High
Malaysia; 2002–2007	High	Low	High	High
Spain; 2014–2017	Low	Low	High	High
Pakistan; 2010–2018	High	Low	Low	High
South Africa; 2015–2017	Low	Low	Low	High
Morocco; 2010–2011	Low	Low	Low	Low
South Africa; 2012–2016	Low	Low	Low	Low
Germany; 2005–2012	High	Low	High	High
Turkey; 2012–2016	High	Low	High	High
Pakistan; 2011–2012	Low	High	Low	Low
Turkey; 2014–2015	High	High	Low	Low
Australia; 2011–2013	High	Low	High	High
Multi–county; 2010–2014	Low	High	Low	Low
Bucharest, Romania; 2016–2017	Low	Low	High	Low
Multi–country; 2013	Low	High	High	High
Georgia; 2014–2017	Low	Low	High	Low
Mozambique; 2014–2016	Low	Low	High	Low
Spain; 2010–2016	High	Low	Low	High
Indonesia; 2013–2016	Low	Low	High	Low
Spain; 2010–2015	Low	Low	Low	Low
China; 2014–2015	High	Low	Low	High
China; 2016–2017	High	Low	High	High
Zambia; 2011–2013	Low	High	Low	Low
South Africa; 2011–2013	Low	High	Low	Low
Bangladesh; 2012–2013	Low	High	Low	Low
Bangladesh; 2012–2013	Low	High	Low	Low

Table A20–2a. hMPV – Risk of bias for community–based studies reporting incidence rates of hMPV–ALRI*

Location; period	Study Design	Patient groups excluded	Case definition	Sampling strategy	Test method
USA; Jan–Dec 2009	Low	Low	Low	High	Low
South Africa; Jun 2012–Dec 2017	Low	Low	Low	Low	Low
Pakistan; Dec 2012–Nov 2013	Low	Low	Low	Low	Low
Bangladesh; 2013–2014	Low	Low	Low	High	Low
Nepal; 2004–2007	Low	High	Low	Low	Low
India; Aug 2012–Aug 2014	Low	Low	Low	Low	Low
USA; 1976–2001	Low	High	Low	High	Low
Peru; Mar 2009 –Sep 2011	Low	Low	High	Low	Low
Australia; Sep 2010–Oct 2014	Low	High	Low	High	Low
Australia; Jul 1996–Jul 1999	Low	High	Low	Low	Low

Table A20–2b. hMPV – Risk of bias for community–based studies reporting incidence rates of hMPV–chest wall indrawing ALRI.†

Location; period	Study Design	Patient groups excluded	Case definition	Sampling strategy	Test method
Pakistan; Oct 2011–July 2014	Low	Low	Low	Low	Low
South Africa; Jun 2012–Dec 2017	Low	Low	Low	Low	Low
Bangladesh; 2013–2014	Low	Low	Low	High	Low
Nepal; 2004–2007	Low	High	Low	Low	Low
India; Aug 2012–Aug 2014	Low	Low	Low	Low	Low

* "Low" for a low risk of bias, and "High" for a high risk of bias.
† "Low" for a low risk of bias, and "High" for a high risk of bias.

Table A19–3c. hMPV – Risk of bias for hospital–based studies reporting hospitalisation rate of hMPV–ALRI *

Location; period	Study Design	Adjustment for healthcare utilization	Patient groups excluded	Case definition	Sampling strategy	Test method
USA; Nov–May, 2003–2009	Low	Low	High	High	Low	Low
South Africa; Feb 2009–Dec 2012	Low	Low	High	Low	Low	Low
Thailand; 2005–2010	Low	Low	Low	High	Low	High
USA; Jan 2010–June 2012	Low	Low	High	Low	Low	High
USA; Aug 2000–Sep 2001	Low	Low	High	High	Low	Low
United Kingdom; Oct 2001–June 2002	Low	Low	Low	High	High	Low
USA; July 2007–June 2013	High	Low	Low	Low	High	High
India; Aug 2009–July 2011	Low	Low	Low	High	Low	Low
Guatemala; Nov 2007–Dec 2012	Low	Low	Low	Low	Low	Low
Kenya; Sep 2007–Aug 2010	Low	Low	Low	Low	Low	Low
USA; Jan–Dec 2009	Low	Low	Low	Low	High	Low
Spain; July 2004–June 2007	Low	Low	Low	High	Low	Low
Thailand; Jan 2012–Dec 2013	Low	High	High	Low	Low	Low
Thailand; Jan 2012–Dec 2013	Low	High	High	Low	Low	Low
Philippines; Feb 2014–Jun 2016	Low	Low	Low	Low	Low	Low
Viet Nam; Jan 2007–Dec 2014	Low	High	Low	Low	Low	Low
South Africa; Jun 2012–Dec 2017	Low	Low	Low	Low	Low	Low
Mozambique; Jan–Dec 2011	Low	Low	Low	Low	Low	Low
Chile; 2012–2013	Low	Low	Low	Low	Low	High
Bangladesh; 2013–2014	Low	Low	Low	Low	High	Low
Argentina; Jun 2008–Dec 2010	Low	Low	High	High	Low	Low

* "Low" for a low risk of bias, and "High" for a high risk of bias.

Location; period	Study Design	Adjustment for healthcare utilization	Patient groups excluded	Case definition	Sampling strategy	Test method
Philippines; Jul 2000–Dec 2004	Low	Low	High	Low	High	Low
South Africa; 2015–2017	Low	Low	Low	Low	High	Low
South Africa; Jan 2000–Dec 2002	Low	Low	Low	Low	High	Low
India; May 2009–Apr 2013	Low	Low	Low	Low	Low	Low
Jordan; Mar 2010–Mar 2013	Low	Low	Low	Low	Low	Low
Kenya; Jan 2007– Dec 2017	Low	Low	Low	Low	Low	Low
Argentina; May 2011–Aug 2013	Low	Low	Low	Low	Low	Low
South Africa; 2010–2015	Low	High	Low	Low	Low	Low
South Africa; 2010–2015	Low	High	Low	Low	Low	Low
USA; Oct 2001– Sep 2003	Low	Low	High	High	Low	Low
Peru; Mar 2009 –Sep 2011	Low	Low	Low	High	Low	Low
Norway; Nov 2006–July 2015	Low	Low	High	Low	High	Low
Mozambique; Sep 2006–Sep 2007	Low	Low	Low	Low	Low	Low
Kenya; Mar 2007–Feb 2010	Low	Low	Low	Low	High	Low
Bangladesh; 2010–2014	Low	Low	Low	High	Low	Low

Table A19–2d. hMPV – Risk of bias for hospital–based studies reporting proportions of hMPV–ALRI*

Location; period	Study Design	Patient groups excluded	Case definition	Sampling strategy	Test method
Brazil; March 2008–Feb 2010	Low	Low	High	Low	Low
Brazil; April 2012–March 2013	Low	Low	Low	High	Low
Thailand; 2005–2010	Low	Low	High	Low	High
United Kingdom; Oct 2004–Oct 2005	High	Low	High	High	Low
France; Oct 2007–Sep 2008	High	Low	High	High	Low
India; May 2011–April 2013	Low	Low	Low	Low	Low
Cameroon; Sep 2011–Sep 2013	Low	Low	High	Low	Low
Oman; Dec 2007–Dec 2008	Low	High	High	Low	Low
China; Jan 2011–Dec 2013	High	Low	High	Low	Low
China; July 2008–June 2010	High	Low	Low	High	Low
Italy; Jan 2000–May 2002	Low	Low	High	High	Low
Brazil; 2003–2006	Low	Low	High	High	Low
USA; Oct 2005–Sep 2007	Low	Low	High	High	Low
Mexico; Oct 2010–Sep 2014	Low	Low	High	Low	Low
USA; Oct 2001– Sep 2003	Low	High	High	Low	Low
Israel; Nov 2001–Oct 2005	Low	Low	Low	Low	Low
Greece; Oct 1999–Sep 2000	Low	Low	High	High	Low
China; Dec 2011–Nov 2012	Low	Low	Low	Low	Low
Italy; 2004–2008	High	Low	Low	Low	Low
China; Sep 2008–Aug 2009	High	Low	Low	Low	High
Viet Nam; May 2009–Dec 2010	Low	High	High	Low	Low
Republic of Korea; Sep 2011–Aug 2012	High	Low	High	High	Low
Japan; April 2007–March 2012	Low	Low	Low	High	Low
China; Jan–Dec 2011	Low	Low	High	Low	Low
India; Aug 2009–July 2011	Low	Low	High	Low	Low
China; July 2009–June 2014	Low	Low	High	High	Low
China; March 2010–Feb 2012	High	Low	High	Low	Low
India; April 2010–March 2011	Low	Low	Low	Low	Low
Australia; Jan 2000–Dec 2005	High	Low	Low	Low	Low
Spain; Sep 2005–Aug 2008	Low	Low	High	High	Low
China; Jan–Dec 2007	High	Low	Low	Low	Low
Poland; Oct 2008–April 2011	High	Low	High	High	Low
Spain; Jan–Dec 2011	Low	High	High	Low	High

* "Low" for a low risk of bias, and "High" for a high risk of bias.

Location; period	Study Design	Patient groups excluded	Case definition	Sampling strategy	Test method
Italy; Oct 2004–Sep 2006	Low	Low	High	Low	Low
China; July 2007–June 2008	Low	High	High	Low	Low
China; Jan–Dec 2011	Low	High	Low	Low	High
China; Sep 2007–Aug 2008	Low	Low	Low	High	Low
China; Feb 2011–Jan 2012	Low	Low	Low	High	Low
Bangladesh; Aug 2014–Jul 2015	Low	High	High	High	Low
Spain; Jan 2011–Jan 2013	Low	Low	Low	High	Low
United Kingdom; 2009–2012	Low	High	Low	High	Low
Cyprus; Nov 2010–Oct 2013	Low	Low	High	High	Low
Iraq; Apr 2011–Mar 2012	Low	Low	High	Low	Low
Mozambique; Sep 2006–Sep 2007	Low	Low	Low	Low	Low
Kenya; Mar 2007–Feb 2010	Low	Low	Low	High	Low
China; April 2006–March 2008	Low	Low	Low	Low	Low
China; 2007–2010	Low	Low	High	Low	Low
Brazil; Apr 2008–Mar 2009	Low	Low	High	Low	Low
USA; Jan–Dec 2009	Low	Low	Low	High	Low
South Africa; 2003–2004	High	Low	High	High	Low
China; Mar 2010–Feb 2011	Low	Low	High	Low	Low
Spain; July 2004–June 2007	Low	Low	High	Low	Low
China; Apr 2012–Mar 2013	Low	Low	Low	Low	Low
China; Apr 2008–Mar 2009	Low	Low	High	Low	Low
China; Jan 2011–Dec 2012	High	Low	High	Low	Low
China; Nov 2005–Oct 2006	High	Low	High	Low	Low
China; Jan–Dec 2010	High	Low	High	Low	High
China; Jan 2009–Dec 2012	High	High	High	Low	Low
China; Oct 2010–Sep 2012	High	High	High	Low	Low
China; Jul 2013–Jun 2014	Low	Low	High	Low	Low
China; Jan–Dec 2014	Low	High	Low	Low	High
China; Jan–Dec 2015	High	Low	High	Low	Low
China; Oct 2011–Sep 2012	Low	Low	High	Low	High
China; Jul 2012–Jul 2013	Low	Low	Low	Low	Low
China; Mar 2015–Feb 2016	Low	Low	Low	Low	Low
China; Mar 2010–Feb 2011	Low	Low	Low	Low	Low
China; Apr 2013–Mar 2014	Low	Low	Low	Low	Low
China; Jun 2009–May 2012	Low	Low	High	Low	Low
China; Jan 2006–Dec 2008	Low	High	High	Low	Low
China; Jan 2011–Dec 2013	Low	Low	Low	Low	Low
Morocco; Nov 2010–Dec 2011	Low	Low	Low	Low	Low
Philippines; May 2008–Feb 2015	Low	Low	Low	Low	Low

Location; period	Study Design	Patient groups excluded	Case definition	Sampling strategy	Test method
Philippines; Sep 2012–Feb 2015	Low	Low	Low	Low	Low
Bangladesh; 2010–2014	Low	Low	High	Low	Low
Thailand; Jan 2012–Dec 2013	Low	High	Low	Low	Low
Thailand; Jan 2012–Dec 2013	Low	High	Low	Low	Low
Iran (Islamic Republic of); Mar 2010– Mar 2013	High	Low	Low	High	Low
Zambia; Oct 2011 – Oct 2014	Low	High	Low	Low	Low
Mali; Jan 2012 – Jan 2014	Low	High	Low	Low	Low
Kenya; Aug 2011–Jul 2013	Low	High	Low	Low	Low
Pakistan; Aug 2009–Jul 2012	Low	Low	High	Low	Low
South Africa; Aug 2011–Aug 2013	Low	Low	Low	Low	Low
Bangladesh; Jan 2012 – Dec 2013	Low	High	Low	Low	Low
Bangladesh; Jan 2012–Dec 2013	Low	High	Low	Low	Low
Philippines; Feb 2014–Jun 2016	Low	Low	Low	Low	Low
Viet Nam; Jan 2007–Dec 2014	Low	Low	Low	Low	Low
South Africa; Jun 2012–Dec 2017	Low	Low	Low	Low	Low
Mozambique; Jan–Dec 2011	Low	Low	Low	Low	Low
Chile; 2012–2013	Low	Low	Low	Low	High
Philippines; Aug 2012–Feb 2015	Low	Low	Low	Low	Low
Bangladesh; 2013–2014	Low	Low	Low	High	Low
Argentina; Jun 2008–Dec 2010	Low	High	High	Low	Low
Philippines; Jul 2000–Dec 2004	Low	High	Low	High	Low
South Africa; 2015–2017	Low	Low	Low	High	Low
South Africa; Jan 2000–Dec 2002	Low	Low	Low	High	Low
India; May 2009–Apr 2013	Low	Low	Low	Low	Low
Jordan; Mar 2010–Mar 2013	Low	Low	Low	Low	Low
Kenya; Jan 2007– Dec 2017	Low	Low	Low	Low	Low
Argentina; May 2011–Aug 2013	Low	Low	Low	Low	Low
Nepal; Jan 2006–Jan 2008	Low	High	Low	Low	Low
Germany; Jan 2010–Dec 2014	Low	Low	Low	Low	Low
South Africa; 2010–2015	Low	Low	Low	Low	Low
South Africa; 2010–2015	Low	Low	Low	Low	Low
USA; 2010–2016	Low	Low	Low	High	High
Philippines; Sep 2012–Jul 2016	Low	Low	Low	Low	Low

Table A19–2e. hMPV – Risk of bias for hospital–based studies reporting in–hospital case–fatality ratios (hCFRs) of hMPV–ALRI*

Location; period	Study Design	Patient groups excluded	Case definition	Sampling strategy
Norway; Nov 2002–April 2003	High	Low	High	High
Brazil; March 2008–Feb 2010	Low	Low	High	Low
Spain; Oct 2000–June 2003	Low	High	High	Low
USA; Oct 2001–May 2004	High	Low	High	High
Cambodia; April 2007–Feb 2010	Low	High	Low	High
USA; June 2007–June 2010	High	Low	Low	High
South Africa; June–August 2002	Low	Low	High	Low
Pakistan; March 2011–April 2012	Low	High	Low	Low
USA; Oct 2005–Sep 2007	Low	Low	High	High
Thailand; April 2002–Aug 2004	Low	High	High	High
USA; Oct 2001– Sep 2003	Low	High	High	Low
Saudi Arabia; July 2007–Nov 2008	High	Low	High	High
Turkey; Nov 2011–May 2012	High	Low	High	High
Mali; July 2011–Dec 2012	Low	High	Low	Low
South Africa; Jan 2010–Dec 2013	Low	Low	Low	Low
USA; July 2007–June 2013	High	Low	Low	High
Viet Nam; Nov 2004–Jan 2008	Low	High	High	Low
Turkey; Oct 2006–March 2007	Low	High	High	Low
India; Aug 2009–July 2011	Low	Low	High	Low
Jordan; Dec 2003–May 2004	Low	Low	High	High
Chile; May 2005–May 2007	Low	High	Low	High
Guatemala; Nov 2007–Dec 2012	Low	Low	Low	Low
Argentina; Nov–Dec 2009	High	Low	High	High
Japan; 37712	High	Low	Low	High
China; Jan 2006–Dec 2007	High	Low	High	Low
Norway; Nov 2006–July 2015	Low	Low	Low	High
Egypt, Jordan, Oman, Qatar and Yemen; Dec 2007–Feb 2014	Low	Low	High	High
Mozambique; Sep 2006–Sep 2007	Low	Low	Low	Low
Brazil; Apr 2008–Mar 2009	Low	Low	High	Low
Republic of Korea; Dec 2003–Feb 2005	Low	Low	High	High
Spain; July 2004–June 2007	Low	Low	High	Low
China; June 2006–June 2007	High	Low	Low	Low
China; Sep 2007–Aug 2008	Low	Low	Low	Low
China; Jan 2009–Dec 2012	High	High	High	Low
China; Jan 2006–Dec 2008	Low	High	High	Low
China; Dec 2006–Feb 2008	Low	Low	Low	High

* "Low" for a low risk of bias, and "High" for a high risk of bias.

Location; period	Study Design	Patient groups excluded	Case definition	Sampling strategy
Morocco; Nov 2010–Dec 2011	Low	Low	Low	Low
Philippines; May 2008–Feb 2015	Low	Low	Low	Low
Philippines; Sep 2012–Feb 2015	Low	Low	Low	Low
Bangladesh; 2010–2014	Low	Low	High	Low
Thailand; Jan 2012–Dec 2013	Low	High	Low	Low
Thailand; Jan 2012–Dec 2013	Low	High	Low	Low
Zambia; Oct 2011 – Oct 2014	Low	High	Low	Low
Mali; Jan 2012 – Jan 2014	Low	High	Low	Low
Kenya; Aug 2011–Jul 2013	Low	High	Low	Low
Pakistan; Aug 2009–Jul 2012	Low	Low	High	Low
South Africa; Aug 2011–Aug 2013	Low	Low	Low	Low
Bangladesh; Jan 2012 – Dec 2013	Low	High	Low	Low
Bangladesh; Jan 2012–Dec 2013	Low	High	Low	Low
Philippines; Feb 2014–Jun 2016	Low	Low	Low	Low
South Africa; Jun 2012–Dec 2017	Low	Low	Low	Low
Mozambique; Jan–Dec 2011	Low	Low	Low	Low
Chile; 2012–2013	Low	Low	Low	Low
Philippines; Aug 2012–Feb 2015	Low	Low	Low	Low
Bangladesh; 2013–2014	Low	Low	Low	High
Argentina; Jun 2008–Dec 2010	Low	High	High	Low
Philippines; Jul 2000–Dec 2004	Low	High	Low	High
South Africa; 2015–2017	Low	Low	Low	High
South Africa; Jan 2000–Dec 2002	Low	Low	Low	High
Jordan; Mar 2010–Mar 2013	Low	Low	Low	Low
Kenya; Jan 2007– Dec 2017	Low	Low	Low	Low
Argentina; May 2011–Aug 2013	Low	Low	Low	Low
Germany; Jan 2010–Dec 2014	Low	Low	Low	Low
South Africa; 2010–2015	Low	Low	Low	Low
South Africa; 2010–2015	Low	Low	Low	Low
USA; 2010–2016	Low	Low	Low	High
Philippines; Sep 2012–Jul 2016	Low	Low	Low	Low

Table A19–3a. hPIV – Risk of bias for community–based studies reporting incidence rates of hPIV–ALRI*

Location; period	Study Design	Patient groups excluded	Case definition	Sampling strategy	Test method
India; 2001–2005	Low	Low	Low	High	High
USA; 2009	Low	Low	Low	High	Low
India; 2012– 2014	Low	Low	Low	Low	Low
Pakistan; 2012–2013	Low	Low	Low	High	Low
Bangladesh; 2013–2014	Low	Low	Low	High	Low
South Africa; 2012–2017	Low	Low	Low	Low	Low
Nepal; 2004–2007	Low	High	Low	Low	Low
USA; 1976–2001	Low	High	High	High	High
Bangladesh; 1993–1994	Low	Low	Low	High	High
Australia; 2010–2014	Low	High	Low	High	Low
Australia; 1996–1999	Low	High	Low	Low	Low
Spain; 1996–1999	Low	Low	High	High	High

Table A19–3b. hPIV – Risk of bias for community–based studies reporting incidence rates of hPIV–severe ALRI. †

Location; period	Study Design	Patient groups excluded	Case definition	Sampling strategy	Test method
Pakistan; 2011–2014	Low	Low	Low	Low	Low
India; 2001–2005	Low	Low	Low	High	High
India; 2012–2014	Low	Low	Low	Low	Low
Bangladesh; 2013–2014	Low	Low	Low	High	Low
South Africa; 2012–2017	Low	Low	Low	Low	Low

* "Low" for a low risk of bias, and "High" for a high risk of bias.
† "Low" for a low risk of bias, and "High" for a high risk of bias.

Table A19–3c. hPIV – Risk of bias for hospital–based studies reporting hospitalisation rate of hPIV–ALRI *

Location; period	Study Design	Adjustment for healthcare utilization	Patient groups excluded	Case definition	Sampling strategy	Test method
Thailand; 2005–2010	Low	Low	Low	High	Low	High
USA; 2010–2012	Low	Low	High	Low	Low	High
Nunavut; 1997–1998	Low	Low	Low	Low	High	High
USA; 2000–2004	Low	Low	High	High	Low	Low
India; 2009–2011	Low	Low	Low	High	Low	Low
Kenya; 2007–2010	Low	Low	Low	Low	Low	Low
Germany; 1996–2000	High	Low	Low	High	High	Low
USA; 2009	Low	Low	Low	Low	High	Low
China; 2003–2006	Low	Low	High	High	Low	High
Spain; 2004–2007	Low	Low	Low	High	Low	Low
Philippines; 2014–2016	Low	Low	Low	Low	Low	Low
Kenya; 2007–2017	Low	Low	Low	Low	High	Low
Viet Nam; 2007–2016	Low	High	Low	Low	Low	Low
Argentina; Jun 2008–Dec 2010	Low	High	High	High	Low	High
Philippines; Jul 2000–Dec 2004	Low	Low	High	High	Low	Low
Jordan; Mar 2010–Mar 2013	Low	High	Low	Low	Low	Low
Gambia; 2012–2013	Low	High	High	Low	Low	Low
Thailand; Jan 2012–Dec 2013	Low	High	Low	Low	Low	Low
Thailand; Jan 2012–Dec 2013	Low	High	Low	Low	Low	Low
Argentina; 2000–2017	Low	High	Low	Low	Low	High
Mozambique; Jan 2011–Jul 2014	Low	Low	Low	Low	Low	Low
Chile; 2012–2013	Low	Low	Low	Low	Low	High

* "Low" for a low risk of bias, and "High" for a high risk of bias.

Location; period	Study Design	Adjustment for healthcare utilization	Patient groups excluded	Case definition	Sampling strategy	Test method
Chile; 2012–2013	Low	Low	Low	Low	Low	High
South Africa; Mar 1998–Oct 2005	Low	Low	Low	Low	Low	High
Bangladesh; 2013–2014	Low	Low	Low	Low	High	Low
South Africa; Jun 2012–Dec 2017	Low	Low	Low	Low	Low	Low
South Africa; 2010–2015	Low	High	Low	Low	Low	Low
South Africa; 2010–2015	Low	High	Low	Low	Low	Low
Germany; 1999–2001	Low	Low	Low	High	High	Low
China; 2007–2008	High	Low	Low	Low	High	High
Canada; 2007–2012	High	Low	Low	Low	High	High
Spain; 2011–2012	Low	Low	High	High	Low	Low
Mozambique; 2006–2007	Low	Low	Low	Low	Low	Low
Kenya; 2007–2010	Low	Low	Low	Low	High	Low
Bangladesh; 2010–2014	Low	Low	Low	High	Low	Low

Table A19–3d. hPIV – Risk of bias for hospital–based studies reporting proportions of hPIV–ALRI*

Location; period	Study Design	Patient groups excluded	Case definition	Sampling strategy	Test method
Brazil; 2008–2010	Low	Low	High	Low	Low
France; 2002–2004	High	Low	Low	High	High
Germany; 1999–2001	Low	Low	High	High	Low
France; 2003–2004	Low	Low	High	High	High
Argentina; 1998–2002	High	Low	Low	High	High
Brazil; 2012–2013	Low	Low	Low	High	Low
Thailand; 2005–2010	Low	Low	High	Low	High
USA; 1996–1998	High	Low	High	High	High
France; 2007–2008	High	Low	High	High	Low
Cameroon; 2011–2013	Low	Low	High	Low	Low
Oman; 2007–2008	Low	High	High	Low	Low
Malaysia; 1992–2008	High	Low	High	High	High
Ghana; 2008	Low	Low	Low	Low	Low
China; 2011–2013	High	Low	High	Low	Low
China; 2013–2015	Low	Low	Low	Low	High
Canada; 2007–2012	High	Low	Low	High	High
Brazil; 2005–2007	Low	High	High	Low	High
Thailand; 2013–2014	Low	High	Low	High	Low
USA; 2005–2007	Low	Low	High	High	Low
Brazil; 1992	High	Low	High	High	High
China; 2001–2006	High	Low	Low	Low	High
Taiwan; 1997–1999	High	Low	High	Low	High
Argentina; 1998–2002	High	Low	Low	High	High
China; 2004–2012	High	Low	High	High	High
China; 2012–2015	Low	Low	High	Low	High
USA; 2010–2014	Low	Low	High	Low	Low
USA; 2000–2004	Low	High	High	Low	Low
Israel; 2001–2005	Low	Low	Low	Low	Low
China; 2010–2011	Low	Low	Low	Low	Low
Italy; 2004–2008	High	Low	Low	Low	Low
Bangladesh; 1993–1994	Low	Low	Low	High	High
Saudi Arabia; 1997–2001	Low	Low	High	High	High
Saudi Arabia; 1993–1996	High	Low	High	Low	High
Saudi Arabia; 2005–2010	High	Low	Low	Low	High
China; 2014	High	High	Low	Low	Low
Viet Nam; 2009–2010	Low	High	High	Low	Low
Republic of Korea; 2011–2012	High	Low	High	High	Low
Japan; 2007–2012	Low	Low	Low	High	Low
China; 2011	Low	Low	High	Low	Low
India; 2009–2011	Low	Low	High	Low	Low
China; 2014–2015	High	Low	Low	Low	High
China; 2009–2014	Low	Low	High	High	Low
China; 2010–2012	High	Low	High	Low	Low
Australia; 2000–2005	High	Low	Low	Low	Low
Mexico; 2002–2004	Low	Low	High	Low	Low

* "Low" for a low risk of bias, and "High" for a high risk of bias.

Location; period	Study Design	Patient groups excluded	Case definition	Sampling strategy	Test method
Spain; 2005–2008	Low	Low	High	High	Low
China; 2007	High	Low	Low	Low	Low
Poland; 2008–2011	High	Low	High	High	Low
China; 2014	High	High	Low	Low	Low
Spain; 2011	Low	High	High	Low	High
India; 2011–2012	Low	Low	Low	Low	Low
Thailand; 1998–2001	Low	Low	High	High	High
Brazil; 1987–1989	Low	Low	Low	High	High
Paraguay; 2009	High	Low	Low	High	Low
China; 2007–2008	Low	High	High	Low	Low
China; 2001–2003	High	High	Low	Low	High
Germany; 1996–2000	High	Low	High	High	Low
China; 2007–2008	Low	Low	Low	High	Low
China; 2011–2012	Low	Low	Low	High	Low
Bangladesh; 2014–2015	Low	High	High	High	Low
Republic of Korea; 1996–1998	High	High	High	Low	High
Spain; 2011–2013	Low	Low	Low	High	Low
United Kingdom; 2009–2012	Low	High	Low	High	Low
Cyprus; 2010–2013	Low	Low	High	High	Low
Egypt; 2007–2014	Low	Low	High	High	Low
Jordan; 2008–2010	Low	Low	High	High	Low
Oman; 2008–2009	Low	Low	High	High	Low
Qatar; 2008–2009	Low	Low	High	High	Low
Yemen; 2010–2014	Low	Low	High	High	Low
Mozambique; 2006–2007	Low	Low	Low	Low	Low
Kenya; 2007–2010	Low	Low	Low	High	Low
China; 2007–2010	Low	Low	High	Low	Low
Brazil; 2008–2009	Low	Low	High	Low	Low
USA; 2009	Low	Low	Low	High	Low
South Africa; 2003–2004	High	Low	High	High	High
China; 2010–2011	Low	Low	High	Low	Low
Spain; 2004–2007	Low	Low	High	Low	Low
China; 2012–2013	Low	Low	Low	Low	Low
China; 2003–2006	High	Low	High	Low	High
China; 2011–2012	High	Low	Low	Low	High
China; 2012–2013	High	Low	High	Low	High
China; 2011–2012	High	Low	High	Low	Low
China; 2014	High	Low	High	Low	High
China; 2014–2015	High	Low	High	Low	High
China; 2011–2013	High	Low	High	Low	High
China; 2013–2014	High	Low	Low	Low	High
China; 2011	High	Low	High	Low	High
China; 2009–2012	High	Low	High	Low	High
China; 2000	High	Low	Low	Low	High
China; 2014–2015	High	Low	High	Low	High
China; 2006–2015	Low	High	High	Low	High
China; 2013–2014	Low	Low	High	Low	Low
China; 2014	Low	High	Low	Low	High
China; 2014–2015	High	High	High	Low	High
China; 2015	High	Low	High	Low	Low

Location; period	Study Design	Patient groups excluded	Case definition	Sampling strategy	Test method
China; 2015	High	Low	High	Low	High
China; 2016	High	Low	High	Low	High
China; 2013–2015	High	Low	High	Low	High
China; 2015–2016	High	Low	High	Low	High
China; 2009–2010	Low	Low	Low	Low	Low
China; 2001–2002	Low	High	Low	Low	High
China; 2006–2007	Low	High	Low	Low	High
China; 2003–2006	Low	Low	High	Low	High
China; 2012–2013	Low	Low	Low	Low	Low
China; 2013	High	Low	Low	Low	High
China; 2010–2011	Low	Low	High	Low	Low
China; 2015–2016	Low	Low	Low	Low	Low
China; 2011–2016	High	High	Low	Low	High
China; 1994–1997	High	Low	Low	Low	High
China; 2007–2009	High	High	Low	High	High
China; 1996–1997	Low	High	Low	Low	High
China; 2005–2007	Low	Low	Low	Low	High
China; 2001–2003	High	Low	Low	High	High
China; 2013–2014	Low	Low	Low	Low	Low
China; 2009–2012	Low	Low	High	Low	Low
China; 2010	High	Low	Low	Low	Low
China; 2005–2006	High	Low	Low	Low	High
China; 2013–2014	High	Low	High	Low	High
China; 2009–2013	Low	Low	High	Low	High
China; 2006–2010	High	Low	Low	Low	High
China; 2013–2014	Low	Low	Low	Low	High
China; 2007	High	Low	Low	Low	High
China; 2011–2012	High	Low	Low	Low	High
Philippines; 2014–2016	Low	Low	Low	Low	Low
Philippines; Sep 2012–Jul 2016	Low	Low	Low	Low	Low
Philippines; Sep 2012–Feb 2015	Low	Low	Low	Low	Low
Philippines; Aug 2012–Feb 2015	Low	Low	Low	Low	Low
Kenya; 2007–2017	Low	Low	Low	High	Low
Viet Nam; 2007–2016	Low	Low	Low	Low	Low
Argentina; Jun 2008–Dec 2010	Low	High	High	Low	High
Philippines; Jul 2000–Dec 2004	Low	High	High	Low	Low
Jordan; Mar 2010–Mar 2013	Low	Low	Low	Low	Low
Bangladesh; 2010–2014	Low	Low	High	Low	Low
Bangladesh; Jan 2012 – Dec	Low	Low	Low	Low	Low
Gambia; 2012–2013	Low	High	Low	Low	Low
Zambia; Oct 2011 – Oct 2014	Low	Low	Low	Low	Low
Thailand; Jan 2012–Dec 2013	Low	Low	Low	Low	Low
South Africa; Aug 2011 – Aug	Low	Low	Low	Low	Low
Thailand; Jan 2012–Dec 2013	Low	Low	Low	Low	Low
Bangladesh; Jan 2012 – Dec	Low	Low	Low	Low	Low
Kenya; Aug 2011 – Nov 2011	Low	Low	Low	Low	Low
Mali; Jan 2012 – Jan 2014	Low	Low	Low	Low	Low
Morocco; Nov 2010–Dec 2011	Low	High	Low	Low	Low
Argentina; 2000–2017	Low	Low	Low	Low	High
Mozambique; Jan 2011–Jul 2014	Low	Low	Low	Low	Low

Location; period	Study Design	Patient groups excluded	Case definition	Sampling strategy	Test method
Chile; 2012–2013	Low	Low	Low	Low	High
Chile; 2012–2013	Low	Low	Low	Low	High
Iran (Islamic Republic of); 2008–	High	Low	High	High	Low
Iran (Islamic Republic of); 2017	High	Low	High	Low	Low
Iran (Islamic Republic of); Sep	High	Low	High	Low	Low
Iran (Islamic Republic of); Jan	High	Low	High	Low	High
Iran (Islamic Republic of); Oct	High	Low	High	Low	Low
South Africa; Mar 1998–Oct 2005	Low	Low	Low	Low	High
Bangladesh; 2013–2014	Low	Low	Low	High	Low
South Africa; Jun 2012–Dec	Low	Low	Low	Low	Low
Nepal; Jan 2006–Jan 2008	Low	High	Low	Low	Low
South Africa; 2010–2015	Low	Low	Low	Low	Low
South Africa; 2010–2015	Low	Low	Low	Low	Low
Germany; Jan 2010–Dec 2014	Low	Low	Low	Low	Low
Philippines; May 2008–Feb 2015	Low	Low	Low	Low	Low

Table A19–3e. hPIV – Risk of bias for hospital–based studies reporting in–hospital case–fatality ratios (hCFRs) of hPIV–ALRI*

Location; period	Study Design	Patient groups excluded	Case definition	Sampling strategy
Brazil; 2008–2010	Low	Low	High	Low
Cambodia; 2007–2010	Low	High	Low	High
Thailand; 2003–2007	Low	Low	High	High
Brazil; 2005–2007	Low	High	High	Low
USA; 2005–2007	Low	Low	High	High
Chile; 2001–2004	High	Low	Low	High
India; 2002–2004	Low	Low	High	Low
Mali; 2011–2012	Low	High	Low	Low
South Africa; 2009–2014	Low	Low	Low	Low
South Africa; 2010–2013	Low	Low	Low	Low
Viet Nam; 2004–2008	Low	High	High	Low
Viet Nam; 2009–2010	Low	High	High	Low
Spain; 1994–2000	Low	Low	High	High
Turkey; 2006–2007	Low	High	High	Low
India; 2009–2011	Low	Low	High	Low
Republic of Korea; 1994–1998	High	Low	High	High
Argentina; 1993–1994	Low	High	Low	Low
Tunisia; 2013–2014	High	High	High	High
Egypt; 2007–2014	Low	Low	High	High
Jordan; 2008–2010	Low	Low	High	High
Oman; 2008–2009	Low	Low	High	High
Qatar; 2008–2009	Low	Low	High	High
Yemen; 2010–2014	Low	Low	High	High
Mozambique; 2006–2007	Low	Low	Low	Low
China; 2003–2006	Low	High	High	Low
China; 2009–2010	Low	High	High	Low
Philippines; 2014–2016	Low	Low	Low	Low
Philippines; Sep 2012–Jul	Low	Low	Low	Low
Philippines; Sep 2012–Feb	Low	Low	Low	Low
Philippines; Aug 2012–Feb	Low	Low	Low	Low
Kenya; 2007–2017	Low	Low	Low	High
Argentina; Jun 2008–Dec 2010	Low	High	High	Low
Philippines; Jul 2000–Dec	Low	High	High	Low
Jordan; Mar 2010–Mar 2013	Low	Low	Low	Low
Bangladesh; 2010–2014	Low	Low	High	Low
Bangladesh; Jan 2012 – Dec	Low	Low	Low	Low
Gambia; 2012–2013	Low	High	Low	Low
Zambia; Oct 2011 – Oct 2014	Low	Low	Low	Low
Thailand; Jan 2012–Dec 2013	Low	Low	Low	Low
South Africa; Aug 2011 – Aug	Low	Low	Low	Low
Thailand; Jan 2012–Dec 2013	Low	Low	Low	Low
Bangladesh; Jan 2012 – Dec	Low	Low	Low	Low
Kenya; Aug 2011 – Nov 2011	Low	Low	Low	Low
Mali; Jan 2012 – Jan 2014	Low	Low	Low	Low
Morocco; Nov 2010–Dec 2011	Low	High	Low	Low

* 1 for a low risk of bias, and 0 for a high risk of bias.

Location; period	Study Design	Patient groups excluded	Case definition	Sampling strategy
Argentina; 2000–2017	Low	Low	Low	Low
Mozambique; Jan 2011–Jul	Low	Low	Low	Low
Chile; 2012–2013	Low	Low	Low	Low
Chile; 2012–2013	Low	Low	Low	Low
South Africa; Mar 1998–Oct	Low	Low	Low	Low
South Africa; Jun 2012–Dec	Low	Low	Low	Low
South Africa; 2010–2015	Low	Low	Low	Low
South Africa; 2010–2015	Low	Low	Low	Low
USA; 2010–2016	Low	Low	Low	High
Germany; Jan 2010–Dec 2014	Low	Low	Low	Low
Philippines; May 2008–Feb	Low	Low	Low	Low

A21. Publications and in press articles related to this thesis

Wang X, Li Y, O'Brien KL, Madhi SA, Widdowson M-A, Byass P, Omer SB, Abbas Q, Ali A, Amu A, et al. Global burden of respiratory infections associated with seasonal influenza in children under 5 years in 2018: a systematic review and modelling study. Lancet Global Health (In press).

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